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FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

AND

THE COLLEGE OF AMERICAN PATHOLOGISTS

INTERNATIONAL WORKSHOP

ON

THE STANDARDIZATION OF

WHOLE BLOOD COAGULATION DEVICES

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1:00 p.m.

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C O N T E N T S

P R O C E E D I N G S

CHAIRPERSON MICHAUD: Good afternoon. We'd like to begin the program, please. Good afternoon. My name is Ginette Michaud and I'd like to welcome you to the International Workshop on the Standardization of Whole Blood Coagulation Devices. We are truly delighted to see the amount of interest that is being generated by this workshop and we thank you all for taking the time out of your busy schedules to participate in today's session.

The U.S. Food and Drug Administration and the College of American Pathologists are sponsoring this event because of the recognized need to standardize the calibration of whole blood clotting assays. We hope in this workshop to facilitate discussions on this very topic. It's clear that participation by all interested parties, which we believe to have here today, is essential to developing a successful standard and we are optimistic that the first step in achieving that goal will be taken here this afternoon.

I want you to please note that the agenda consists of an initial plenary session during which we will be hearing from our panel speakers. This will be followed by working sessions in breakout groups during which you will be asked to generate a standardization proposal.

Our guest panelists were kind enough to generate preliminary proposals of their own and several of these drafts and reactions to them were recently posted on our workshop web site. We urge you to consider the contents of these documents as well as the speakers' presentations in developing a project proposal this afternoon. We hope that our panelists' preliminary work will help focus your discussions and perhaps be a starting point for the proposal generated by this workshop.

Following the break-out sessions, we will be reconvening here in the Washington Room. Each discussion group will be asked to share the recommendations of their participants with the general assembly. This will be followed by a public comment period and I ask that any individual wanting to make remarks during the public comment period, I ask that these individuals identify themselves to me as early as possible so that we can allocate time for their remarks.

Finally, our closing speaker will summarize the afternoon's achievements which I hope will be many. Before we start our program, I want to acknowledge the work of the organizing committee and the work of many individuals who made this meeting possible, and in particular I want to thank Dr. Sheila Murdock of the Food and Drug Administration

and Dr. Douglas Triplett of the College of American Pathologists for their many, many efforts.

One final note before we begin. You may have noticed in your folders that we have an evaluation form printed on bright yellow paper. We ask that you take a very few minutes to give us your reactions to the workshop so that we can improve future meetings. This is expected to take you only a moment and so that we hope that you can do this for us and return the completed form to the registration desk on your way out this afternoon.

And so without further delay, it's truly an honor to introduce to you our opening speaker, the Director of the Center for Devices and Radiological Health at the U.S. Food and Drug Administration, Dr. David Feigal. Dr. Feigal.

DR. FEIGAL: Thank you very much. It's been a long time since I've been able to actually start out a talk saying "when I was intern," but as an internist, when I began my internship at University of California-Davis, they gave us a kit when we started and one of the things they gave us were two little tubes that contained a small amount of clay in the bottom of them, and I had never used those before and asked what they were and they said, oh, those are for your activated clotting times when you monitor your patients with heparin. That's a test that Dr. Paul Hattersley who is a hemo-pathologist here is particularly

interested in using instead of the other tests that competed with it. And at that hospital was the last time I used that test. And it's interesting--there are some times in your career you think you're never going to see an issue or have an issue come back again and years later the issues are still there.

Let me speak just a little bit about the regulatory framework and the importance of these kinds of meetings to the Food and Drug Administration. If you look at the framework in which products are approved, many times each product develops methods of identifying what its unique contribution is. If it's a drug, if it's a biological product, if it's a device, exactly how does it perform, how does it work? But there are areas where instead of basing the application on the uniqueness of the application, we tie the approval or we tie the understanding of the product to well recognized standards and the standard has obvious advantages.

For some products, it's a starting point. The standards may be standards of good manufacturing or standards of good clinical practice, but there's others where the standards actually relate very closely to how the products perform themselves and that's particularly useful when they're a related group of products that are all trying

to accomplish the same thing. And in the common evaluation of tests, when there is a method that is viewed as the best, there's the phrase "gold standard" that's used in those kinds of settings.

FDA's job often is to evaluate claims about products and the claims really relate to what they do. If the claims are performance based, then much of that work is simplified both for us in evaluating what the claims are and for the manufacturer or the hospital or the clinic that's trying to assert those claims.

There are other times when the claims have to be grounded in clinical relevance. For diagnostics, that's often measured in the kinds of performance measures of reliability, the accuracy of the tests, the ability of those tests to predict things, and the clinical context, the clinical correlation of those.

This is an international meeting so some of the comments about regulation may be a little focused on the United States setting. In the U.S., the regulation of diagnostic tests is complex. The Food and Drug Administration has a clear responsibility for manufacturers of diagnostic tests. Hospital laboratories, clinic laboratories come under the purview of accrediting bodies of the professional societies sometimes who are working in cooperation with the accrediting bodies, sometimes state

licensing authorities, other times groups that are involved in reimbursement such as HCFA. So at the hospital particularly the regulatory framework is particularly complex.

And then the tests, of course, are used in clinical practice and that is predominantly a state concern only in the practice of medicine and the practice of clinical pathology.

What blurs all of these boundaries is when the test moves from the hospital laboratory into the clinic laboratory, to the bedside, the hospital bedside, or to the home where the types of typical reference standards and controls that can be used in the highly controlled environment of the clinical laboratory changes to points where the care is actually delivered. And then not only is it more challenging in a practical sense to make sure that the test is high quality, but is also blurs all of the regulatory distinctions as well.

This is an international meeting and we welcome it being an international meeting, and meetings that deal with standards are particularly relevant for the international regulatory framework. The Center for Devices and Radiologic Health has been an active participant in the global task force, harmonization task force, that has worked to making

the rapid approval and evaluation of devices harmonized worldwide and a key part of that process is by having consensus standards where we can have them.

So I would like to just conclude my remarks by welcoming you, by again reiterating how important this process is to us, and the positive effect that meetings such as this have on the public health when they improve the way that we understand these types of diagnostics and how they improve the practice of clinical medicine. Thank you very much.

CHAIRPERSON MICHAUD: Thank you, Dr. Feigal. At this point, we'd like to directly proceed with our panel presentations. The first panel represents the in vitro diagnostics industry and our first presenter is Mr. James Hill.

Mr. Hill is a principal scientist and coagulation point-of-care systems expert at Roche Diagnostics in Mannheim, Germany. He obtained a bachelor of science degree in biology in 1974 at the Florida Institute of Technology and also completed masters level coursework in the same institute.

Mr. Hill has worked extensively in the area of coagulation, first at Dade, where for close to 11 years he focused on quality assessment and research and development of coagulation assays. He subsequently took a position at

Biotrack where for the next five years he focused his attentions on that device. In 1989, he began work on the Boehringer Mannheim CoaguChek Systems and their standardization. He continues this work to this day. Mr. Hill is active in the ISTH and the American Heart Association.

MR. HILL: Well, thank you. Good afternoon, everybody. I'm really honored to be here. I want to thank the FDA and the HIMA and also my own company for inviting me here. The topic of my talk is "Plan of Action for PT-INR Device Standardization and Evaluation." I believe the key question here is not just standardizing whole blood devices but a little more than that. It's INR-PT standardization, but it's also how to evaluate these devices to ensure the safety for the customers.

That's just a rehash of what Dr. Michaud just talked about so I've been doing finger sticks, PTs and aPTTs since 1985 so I guess I was one of the first ones to get involved with this. And I'm not sure if it's because I like challenges or whether I really like the mountains out in California, but one thing led to another and it looks like it's here to stay.

As far as the standardization and evaluation, in my mind, it's really important to understand the scope, and

does this include standardization and evaluation of plasma devices as well or reagents or instruments? I would think it should because when I got into this work in '89 I realized that I could not necessarily rely on the INR standardization of the current plasma systems that were in the hospital. I had to fine-tune those and validate them because of the variation in instruments and the reagents.

Also, it's very important to define an acceptable INR system error and methods of analysis. I've presented in the past on this. In my handout at the end, I have a little abstract on how to analyze INRs. There is just one way. There's different methods. But we must understand how to evaluate these comparisons. What is good? What is not so good? We need to have some agreement here.

Next, the way I see it we've got a lot of agencies out there. Many of them feel that they are expert in INRs and PTs and devices. I'm not even sure what the EDMA is. I don't want to offend anybody. Maybe it's a typo. But I get very confused there are so many. We need to select the agencies that truly have experts in this area and representatives that will contribute and then we need to solidify these groups because there's some excellent work going on that should be participating in this effort to understand INR standardization and evaluation and hopefully that could be accomplished over the next year or so or less.

We should adopt an ISTH sponsored protocol for INR standardization of new devices and reagents. With the agreement of the experts, this would be more or less a generic version which would be suitable for the different companies who have slightly different products and different needs but follow the basic premises of the WHO INR standardization. It would be really nice to consolidate a keeper of these world standard reagents here in the United States.

I spent a lot of effort trying to order these materials from Europe. I had to write protocols. I had to beg and borrow and thank goodness they trusted me in what I was doing so I was able to secure them. But it's going to be more and more difficult in the future for other companies to get a-hold of these and train the people how to use them and how to do these studies. So it would be nice if we had one keeper right here in the United States.

And finally we've got training and certification for use of these standards and whether that includes the tilt tube method I'm not sure, but really that's what it is right now for the INR. I cannot go across town to a hospital lab and assume that their plasma thromboplastin reagent with their particular instrument is going to give me a standard INR answer. I must go to these world standards

and I must know how to employ them, how to handle them and how to test them.

Some additional considerations other than standardization. It would be nice if we had an expert derived protocol for investigating INR disagreements. We've got enough physicians in here and experts who manage patients on a routine basis. They know it's difficult. They know it's dangerous. They know what's acceptable. They know when to get concerned. Also, this would include during development of a system. When you have disagreements between your whole blood device or a world standard or a typical lab method, what do you do to try to resolve which one is correct or why the discrepancy is taking place? These studies should be done in-house and completed before submitting 510 K studies for clinical evaluations so that there are no surprises later.

When you do decide to employ a referee referenced system, it would be nice if you could use the same citrate plasma that was obtained to do the lab method so that you could do a third method with that. You don't want to get invasive and have to draw the patient's blood yet again in a fancy anticoagulant and ship it off.

And again what level of disagreement really would require such investigations? I was kind of fanatical in the beginning. I was so nervous. I was investigating every

disagreement whether it was eight to ten percent and I was getting overwhelmed with the amount of work I had to do until I sought some help from some physicians and realized that this really does happen. You're going to have disagreements between one system and another regardless of whether it's whole blood or plasma.

And finally, this may drive some of the physicians a little crazy, but I thought I would throw it up here anyway because this is going to come up in the future for devices which do whole blood INRs and PTs and self-testing. You're going to have cases where this whole blood INR is different than the lab INR. And it's not necessarily true that the whole blood INR is incorrect. It may be that the lab INR is incorrect. I'm sorry but I've seen this. I've seen this in several occasions. The point I'm trying to make is that if you have a difference in the INR and it's consistent and you precision of the system, and this would also include a human-based thromboplastin versus a rabbit based thromboplastin, there could be a real consistent difference in the INR within one particular patient.

Now do you shift that INR range so you don't change the dosage or do you go ahead and rely on the new system, make the changeover and make the dosage adjustment? It's something that will come up and it would be nice if we

had a forum of experts to get other opinions on this. And that pretty much concludes my talk so there should be time for a few questions if anybody would like to question the finger-stick PT guy on standardization and calibration or evaluation. Okay. Thank you.

[Applause.]

CHAIRPERSON MICHAUD: Thank you, Mr. Hill. Our next speaker is Dr. Frank LaDuca. Dr. LaDuca is the Vice President of Clinical and Regulatory Affairs at International Technidyne Corporation. Dr. LaDuca holds a doctorate in pathology with a hematology specialty from the State University of New York at Buffalo.

Following a two year NIH-sponsored appointment at the Johns Hopkins Hospital, Frank joined ITC. Dr. LaDuca has worked for more than 20 years in laboratory and point-of-care based coagulation diagnostics and in clinical applications of these devices.

He has developed several point-of-care products and actively presents scientific papers and publishes in the area of hemostasis. He is an active member of several societies including the American Society of Hematology, the American Heart Association, the ISTH, the AACC and also specialty cardiology organizations. Dr. LaDuca.

DR. LaDUCA: Thank you, Dr. Michaud. I will provide a little orientation first. Jim, Pat and myself--

Pat Mize, the gentleman at the end of the table--represent the industry's perspective on this topic that the FDA organized and we have had the opportunity for the course of the past ten days to communicate our presentations to other members of industry. And we've elected to approach this topic on an assay by assay basis. So with that introduction, my topic is the oldest, ACT, the oldest point-of-care coagulation test. I'm very pleased to see that Dr. Feigal actually knew who Dr. Hattersley was and knows that there is clay in the bottom of the tube and that represents the real foundation of point-of-care testing.

Back then in his days, those weren't point-of-care tests. Those were just bedside tests. So I'm going to focus a little bit on ACT and what questions need to be answered in order to achieve standardization of that test.

Jim has already presented some information on the PT and Pat will address the aPTT. I will touch briefly on heparin concentration measurements as an adjunct to ACTs. ACTs are not heparin concentration measurements. They are heparin effect measurements.

Now, we have here a summary of what is currently the state of the art in terms of standardization and reference material. For the PT, Jim has shown the INR

system in somewhat detail in terms of what his open questions are and where its direct application is.

Thankfully, for the PT, while it may not be perfect, there is a plasma laboratory method and there indeed is a reference standard, that is the INR. For the aPTT, there are certainly multiple plasma systems. Every single reagent and instrument test system put together creates yet a new type of aPTT, and there really is no reference. I think there are some members of the panel who could tell you about the trials and tribulations the ISTH has had for the past five or six years trying to establish aPTT standardization.

For the ACT, there is neither a plasma method nor a reference method. And when it comes to heparin concentrations, whether they're measured in whole blood or measured in a laboratory, there is a plasma reference method, the historic reference being protamine titration and there are corollaries to the current measurements of anti-Xa and anti-IIa.

A historical perspective is important. Hattersley started in 1966 taking clay, mined celite, diatomaceous earth, and putting it in test tubes and adding blood. The consequence of that was to create a standardization of the earlier test called the Lee White Clotting Test. Now I know there are some people out here who have actually done Lee

White clotting times. Dr. Feigal is nodding his head. And that test took somewhere around 11 or 12 minutes, a little bit cumbersome, three separate glass tubes, no activator, add blood in the tubes and do sequential clotting times.

It was generally used as its first approach as a screen for coagulation abnormalities. In later years, it became a heparin sensitive test and used for heparin monitoring. But it was in the early 1970s when a couple automated systems came to be, automated, the method by which the clot detection took place, and it was at that point that Hattersley's manual method where he added blood to test tubes and merely incubated them in a 37 degree water bath and tilted them became an automatic clot detection system.

Now today we have several different systems. I put the question mark next to Coaguchek Pro because my colleague out here, Dave Phillips, would not reveal to me one Coaguchek Pro without an ACT. But I know it's similar. But there are certainly many ACT varieties that are available and the Hemochron ACT, which my company manufactures, is one of the oldest ones. It goes back to the early days in first applying Hattersley to an automated system.

The standardization, if one wants to approach it back to its basic roots, would consist basically of these

kinds of parameters. First of all, diatomaceous earth is the first substance that was employed. Clot detection originally manual and quickly adapted to automated. The most critical question that everyone has to have answered when they look at standardization is what is the clinical application? It was questions of clinical application that drove the INR standardization. That was the reason why PT clotting time seconds were no longer helpful because the PT seconds could no longer be used to guide therapy.

Clinical applications of ACT directly relate to when one achieves what they believe to be protective anticoagulation of patients undergoing procedures, cardiac surgery, interventional cardiology. And there have been methods described and there have been standard target times applied for both those arenas.

There are a variety of ACT systems, variety of activators, and a variety of methods to put the activators in the test media, dry or liquid, and a variety of clot detection techniques. The key is that when one has a system, an activator plus the test clot detection method, it is important to relate it to the standards that have existed for clinical maintenance and clinical application.

Now, if one approaches that question with this in mind in terms of how does one standardize as time goes on, that all ACTs create universal direct clinical meaning, it

is important that we recognize the heparin sensitivity issue is the key issue. If you have a different activator, if it's glass or if it's kaolin or diatomaceous earth or micronized silica, you have a different degree of activating of the coagulation cascade and you have different clotting times.

They all aren't equal and they don't need to be equal. But for the purpose of clinical application, they need to have correlations to one another such that clinicians know what the appropriate target is for the test being employed. Additionally, interfering substances is very important. For example, with diatomaceous earth, the basic original Hattersley ACT, if you use a protamine in a patient, Traceall [?], to provide postoperative protection, the diatomaceous earth ACT gets prolonged greatly and is no longer reflective of anticoagulation. So the kaolin ACT is used. Are kaolin ACTs and diatomaceous ACTs the same? They're not. They produce different clotting times, sometimes subtle differences.

But the importance is if you have a kaolin ACT, how does it relate to the diatomaceous earth ACT target times that have been established and utilized in clinical medicine for well over 20, 25 years? The comparisons that are not critically important are shown here.

It's not important for ACT standardization to know the heparin level or to have a correlation to Prothrombin Fragment 1.2 or Fibrinopeptide A . But they are all friends of mine, and I think they have very valuable application. They do not become the standards for ACT. They become standards for--they may be different point-of-care tests and they have different standards, but they are not ACT surrogate standards.

The standardization approach--I'm basically reflective of what Jim said--first, of course, to establish the committee and identify the issues. I think this is the first step. I think that FDA has done well to at least assemble the right group of people to talk about it on a first-time basis. And then to establish a standard material. And that material I would prefer it referenced back to the original Hattersley method. And identify a keeper of the standard. I think that Jim referred to that also. Whether it's national or international, someone that can maintain the materials and the method as a standard. It doesn't mean that every ACT has to be the same as the standard. It has to have relationships to the standard.

And when I say define maintenance and reverification, I'm referring to a couple of levels. First, the manufacturer's level. You know, maintaining adherence to target times that they have achieved over the course of

time. So that a 400 second or 480 second ACT today means the same as it did five years and ten years ago. And secondly, that the institute that holds the standards has the obligation to ensure that they are recalibrated, reverified on a regular basis so there's been no drift.

The alternate, point-of-care test, this goes beyond ACTs. These tests are very important in the same clinical environment. They do not have to fall under the same standardization criteria as ACTs but there should be some methodology to approach standardization of any one of these tests. There are in existence today alternatives to traditional ACTs. There are tests which are not ACT related at all such as thrombin time. And there are specific heparin concentration tests that are available, each of which needs to have, if we're going to do this right, a corresponding standard which can be kept and maintained. And I think in the future, we'll see some of these novel assays being developed, the Prothrombin Fragment 1.2 and Fibrinopeptide A.

This is my summary slide and my keys to standardization. First, to identify the appropriate standard method that can be kept and maintained; to identify a reference standard material; most importantly--I can't overemphasize this enough--the clinicians whom I work with

and whom we all work with on a regular basis establish and maintain clinical application guidelines and make sure those do not change in the future without the clinicians knowing it so they can adjust appropriately. It doesn't preclude the development of new novel tests with new guidelines. It just means those guidelines have to relate to the existing guidelines so patients can be maintained properly and are protected. And that's the provide for future assay development. Are there any questions? There is a copy of my slides on the table outside the door. Thank you.

[Applause.]

CHAIRPERSON MICHAUD: Thank you, Dr. LaDuca. Our next speaker for industry is Dr. Patrick Mize. Dr. Mize is a principal scientist at Cardiovascular Diagnostics, Incorporated. He has over 25 years of industrial experience of which the last 15 years is in developing in vitro diagnostic products including point-of-care immunoassays for Influenza A, RSV, HSV, and the development of fluorescence-based substrates for tryptophanase and beta-lactamase.

Dr. Mize has developed novel point-of-care blood coagulation assays, including the Ecarin Clotting Time test for monitoring of recombinant hirudin, a low range fibrinogen test for the monitoring of the effects of Ancrod, and a whole blood anti-Xa assay for monitoring low molecular weight heparins. His development experience includes the

current whole blood activated Partial Thromboplastin Time offered by Cardiovascular Diagnostics. Dr. Mize.

DR. MIZE: Good afternoon. I appreciate this opportunity to come talk and that the FDA invited the industrial speakers to talk. My particular subject is going to be on aPTT. Again, as Frank said, each of our companies has interest in the other whole blood coagulation devices and we thought it would be best if each one of us took a particular test and spoke to that.

As all of you or many of you know, the aPTT is used for a really diverse number of indications. It's a screen for the intrinsic coagulation cascade and factor deficiencies. I think for the purpose of this meeting today, what we're talking about is how the test could be standardized for the monitoring of heparin. And this is heparin and what I call the therapeutic level, which is less than one unit per ml in the blood. There are other uses of this test including detection of lupus anticoagulants and looking at some of the novel thrombin inhibitors that we know today. And I think when you look at the test, it's really a global assay. It's a family of products. When you look at what the industry offers the clinician, many companies have two or three different aPTT products optimized to detect certain types of clinical conditions.

And I sort of consider that the aPTT is the coagulationist hammer. It's the tool that they use that they have at their disposal to try out when new things need to be done in the laboratory. I don't want to go over this all the way, just to say that the aPTT does measure a whole host of different factors. For it to work properly and for the intrinsic cascade to work properly, you have to have a surface for the initiation, there is calcium involved for the clotting to occur, and that phospholipids are very important. And this is just to emphasize the diverse nature of what you are testing for and the complexity of this system.

Because you need a surface for the initiation, there's many types of surfaces used in this. This is what I call particulate. It could be kaolin, MgAl silicate, celite, and micronized silica. Sometimes in place of the particulate, ellagic acid is used for the activation. The phospholipids in this reagent come from a number of different sources. Most recently, a number of companies have used synthetic phospholipids to hope to develop a more consistent test.

I'd like to again emphasize the different nature of the tests that you're looking at. When you look at a plasma based aPTT, it's really a two-stage assay where you take the plasma and you put it in conjunction with the

sample, the reagent, and you let that activation occur, and that's putting the phospholipids with the surface and this is either two to five minutes long, and then you add calcium to start your clotting reaction to occur.

When you're looking at the whole blood base system, because we're trying to make the system user friendly, that the end-user doesn't have to do a plasma separation, we don't want them to have to do two-stage assay, it all occurs at one time. Both the activation and the initiation of clotting with calcium happens at one time and this is really different than what happens with the laboratory system. And so direct comparisons from the results that you get from this are sometimes very hard to do.

Another thing that I'd like to really emphasize is when you do a separation, you separate your cells from your plasma, you're separating components that are really intimately involved with the coagulation process. So you're really changing what is happening and the whole blood device manufacturer would like to think that we should actually be the gold standard because all the parts of the coagulation cascade are present there, all the cells are there, and when you take those away and you're just looking at the plasma portion of it, you're not really looking at the system. And

again when you do this separation, a lot of times you're concentrating drugs into the plasma or you're eliminating. So really what is happening is changing between the two sample types.

When I talk about calibration and a lot of manufacturers when they talk about calibration, they're really talking about consistency and they're talking about calibrating a new lot of reagents to be the same as the referenced lot of reagents that they have in-house. And this is done by a number of different methods. For aPTT, there are recommendations on how to determine what your normal range is from NCCLS. The heparin response is normally gotten from testing of clinical samples. And this really defines your reagent and is really what you're trying to determine for consistency.

Other things that you will determine and put in the package insert is what the factor sensitivity is and then ultimately you may look at other properties like lupus anticoagulant or response to thrombin inhibitors to fully characterize your product. And what we're trying to do with the manufacturing calibration is be consistent because our customers hate surprises and whatever the product is that they're getting, they want the product to be the same from last month to this month when they get a new lot of material.

So when we talk about standardization with the aPTT, what are we standardizing? As we've seen, we have a family of tests here. They have multiple uses. When you change the reagent, perhaps to standardize it, this is going to affect all the uses and the response that you get and really trying to optimize for one particular analyte with this type of test might negatively affect the other uses.

In the plasma-based systems, an INR-like system for standardization has been attempted and this has shown site-to-site variability. So the INR approach, at least for plasma-based systems, has not been really useful yet for aPTT.

I still think that, you know, we should go through the exercise of trying to use an INR-like system for the whole blood devices. The whole blood devices are very unique from two aspects. One is they minimize the pre-analytical effects that go on. Two hospitals may collect blood in different tubes or spin them down at different times or hold them different amounts of time and this sort of exaggerates what would happen pre-analytically before you test the sample. Using the whole blood sample, you minimize some of these pre-analytical differences and you may get a more consistent result from institution to institution.

We feel like all manufacturers should participate in this because each one of them has a specific device reagent coupling and this won't change from hospital to hospital, which might eliminate some of the differences you see in plasma-based systems when you use a reagent on different types of analyzers so the whole blood aPTT INR approach may work out better.

In conjunction with this, if one has to develop controls or standards to further analyze what is going on, talking to the other industrial representatives, these controls if they're going to be used on our system should have cellular-like components and many of our systems key on what is happening to the red blood cells or other components of the system to detect when clotting occurs. And so this would have to be a part of the control.

You would need normal and abnormal samples for unfractionated heparin to see what your slope is and perhaps instead of getting one defined response in clotting time, a range could be adopted or ratio of ranges at first and see how this works.

If we want to go to factor standards to look at factor deficiencies, these really need to be multilevel in nature to look at the inflection point of where your assay or test starts detecting this factor deficiency.

So I have a conclusion slide for the industry speakers. We really feel that PT standardization is possible. Let's do it. APTT we should pursue it, but this will be a very challenging field, and ACT, it would be very beneficial, but this is just starting. Thank you.

[Applause.]

CHAIRPERSON MICHAUD: Thank you, Dr. Mize, for your remarks. This concludes the presentations by our industry panel. We're next going to hear from the panelists who will be presenting the viewpoints of coagulation experts and end-users of these devices. Our first presenter is Dr. Jack Ansell. Dr. Ansell is Professor of Medicine and Vice Chair of the Department of Medicine at the Boston University School of Medicine. He has over 25 years of experience and interest in the management of oral anticoagulation and the application of new models of management, especially patient self-testing. Welcome, Dr. Ansell.

DR. ANSELL: Thank you, Dr. Michaud. It's a pleasure to be here today to be invited to this presentation and I just want to share with the audience the fact that I was known as the best Lee White clotting time performer as a medical student. That's the only thing I remember from medical school. I've forgotten everything else, but residents always had the medical students do the Lee White

clotting time. I had not made it to the Hattersley test. It was even before that.

And that actually brings up an observation I was thinking about just listening and that is when you think about some of these old tests, particularly Lee White clotting time and other tests, over the years, it's just amazing that our patients by and large do pretty well.

[Laughter.]

DR. ANSELL: You know maybe they're doing better now than they were, but by and large, they do pretty well. And you wonder why. But in any case, it really brings me to my first slide. What I am going to talk about is the prothrombin time and the whole blood, capillary whole blood prothrombin time. And I want to do something a little different and that is I want to start at the end and then maybe work backwards or go back to the beginning because I want to frame the discussion keeping in mind what the end result is and what we're looking for, what we're trying to achieve here in terms of calibration, and that is good clinical outcomes.

And if we cannot figure out how to calibrate and how to standardize, but we still get good clinical outcomes, I think that's still okay. We shouldn't lose sight of that and so if I can have the first slide. I just want to start with one slide that summarizes some of the studies looking

at patient self-testing. And my focus is on point-of-care prothrombin time testing but really in a patient's hands.

And so I'm not going to go into detail here, but as many of you know, the instrumentation that was suitable for patient self-testing was introduced in the late 1980s, 1987 by Lucas, and then a whole series of studies, about eight or nine or ten there, were done over the next ten years that looked at how well patients did. And this is in spite of some of the things that we're talking about here, although no doubt the industry has been very interested and has devoted a lot of time on calibration.

But Rich White in 1989 did a small pilot trial, randomized control, 23 patients, showed that these patients did better than a control group at least in terms of a time in therapeutic range. These are patients on warfarin and that this group was too small for hard outcome differences. I did a study that I reported in 1989 that looked at the issue of patient self-management. Could patients not only test their own PT, but actually manage their own warfarin dosing? A small pilot trial of 20 patients, and in fact, they did very well with excellent time in range. There was not a control there.

Dave Anderson presented in '93 a patient self-testing study, looked at cohort of 40 patients over two

years, showed that (1) the patients were able to do it; and (2) that it correlated fairly well with standard laboratory testing. I reported a seven year follow-up on the initial cohort that was managing their own therapy for seven years, compared it to a matched age and diagnosis matched control group looking back, and found out that, in fact, the patients spent much more time in therapeutic range and did well. Again, there were no differences in hard outcomes.

Dr. Bernardo presented some of the results from Germany where there's extensive patient self-testing going on and this was a retrospective review of 200 or so patients, again more time in therapeutic range if that is a reasonable surrogate for good outcomes.

Dr. Horstkotte from Germany did a randomized control trial of 75 patients with mechanical valves and showed more time in therapeutic range versus the usual care and usual management of warfarin as well as reduced adverse events.

Michael Hascenkam did a study, 21 patients, similar type findings, although again a very small trial. Rebecca Byeth in 1997 in 162 elderly patients, patient self-testing, showed that they spent more time in therapeutic range and, in fact, had fewer adverse events. Sawicki in 1999 just published results from Germany on 90 patients, similar type findings, more time in therapeutic range, no

differences in hard outcomes. And Dr. Koerthe, his study is currently in press, approximately 600 patients he reported on, compared to usual care, more time in therapeutic range and reduced adverse events.

So in spite of everything that we're talking about here, here is a technology that has come about at least on these preliminary studies, and as you can see in the late '90s, starting to get into large randomized control trials with many more patients, and I think there is still a way to go with these studies, but, in fact, we have evidence that whatever it is, it's working, it's valuable, it's standardized, maybe not ideally standardized but, in fact, it does work, and I think we have to think about what we're talking about today in that context and not make a system that is so difficult, so complex, that it is not user-friendly or not useful for the clinician.

Now, what I'd like to do in the next three or four slides, and I hope I get the award for the fewest number of slides here today, and that is I just want to point up a couple of fundamental differences and questions and things that we should think about and I actually will make a suggestion at the end. But some of the fundamental differences between point-of-care, capillary whole blood PT testing, and standard testing is obviously that you're

dealing with whole blood versus plasma. First of all, it's a non-anticoagulated specimen versus an anticoagulated specimen, and what differences does that call for or account for? I can't say at this point in time, but it's something that really needs to be taken into account.

The other thing is that we're dealing with single use sample. In other words, a capillary sample, you can't test it 100 times over the same drop of blood, and every time you retest, it's a new new sample. So when one thinks about the World Health Organization format and other things where tests are done simultaneously on the same sample of blood and there is a very good correlation and CV of the various samples, it may well be different in whole blood monitors because we're dealing with a new prothrombin time every single time that we test.

And as many people have said, no gold standard, and in fact there is no gold standard unless one accepts the plasma PT as the gold standard and that may well be appropriate, but there is no whole blood gold standard.

The other thing is the end point measured. Again, this is a plasma equivalent PT as opposed to a real PT. Now, a number of the speakers already have hinted to the fact that what is the real PT? Will the real PT please stand up because I'm not sure that the plasma PT represents the real PT. However, it is the test that we've used for

the last 60 or so years since the mid-'30s. We have this tremendous experience with it and standardization and so forth. So I think we have to accept that as the real PT, but in reality, the whole blood PT may be closer to what really happens than the plasma PT.

And also, we have to think about the quality of the reagent in the whole blood monitors. At least the way I think about it, the quality of the reagent loses its significance, loses its importance, not to say that it's not important, but it is a whole different level of importance, because we're dealing with a mathematical formula, we're equating an artificial whole blood time back to a plasma PT time, and the reagent that's there in terms of what the original ISI of that reagent is may not be important, although the one that is applied to it ultimately will be important.

And then also multiple technologies we're dealing with here. We have whole blood monitors that measure the end-point and some type of clotting assay or thrombin generation assay or electrical impedance assay or various other ones. And new ones are coming out or are in development. So this is similar to the types of instruments that we have to deal with with plasma PTs where we have all different types of technologies.

I think there are a few fundamental questions that we need to think about and I would like to really move back a step and get back to the derivation of the initial correlation formula and how is that derived. I think it's something to consider in our discussions here and not just the calibration of new lots of thromboplastin or new cartridges as they come out, but how does the manufacturer initially correlate their instrument with standard PTs? What is the standard and the reagent that they compare it to? Should it be the World Health Organization standard, the international reference, and a 60-20 full scheme standardization, or something else? What type of sample is going to be used in the whole blood monitor? A capillary sample or a venous sample? Because both have been used.

How many data points does one need to derive that initial equation, that initial formula? Do you need simply 60 points or 80 points or do you need two, three, four or 500 points? What's the range of INRs that need to be tested in order to develop that correlation? Pretty much the therapeutic range or do you need a very wide, wide range?

And the quality of the thromboplastin--does it really matter? And I think that is an important question. And then you jump down. Once you have established an instrumentation and a methodology that is correlated to something, then the question is calibration of new lots of

thromboplastins and again whenever we mention thromboplastin with these instruments, it's really a thromboplastin cartridge combination. But does one simply repeat the initial procedure? Does one use the WHO procedure? Does one adjust the formula to account for differences in the thromboplastin or adjust the ISI of the thromboplastin to account for differences and so on? And then there's the effects of the cartridge as well as the thromboplastin.

And then finally, there are a number of operational questions that one needs to consider in terms of point-of-care testing. The skill of the tester. First of all, we have professional use in a hospital or office setting versus non-professional use by patients themselves. We have individuals doing frequent tests, 20, 30, 40 a day, versus infrequent tests, perhaps once a week. Does that make a difference?

We have the environment of testing which may be a factor. The hospital is one environment, usually fairly controlled, but not always. The office environment, and then we have the home environment which is relatively uncontrolled. We have the whole issue of quality assessment and quality control, which I don't know that we're going to discuss today necessarily, but that's the whole next step, and that once you have calibrated and standardized your

instruments, what do you do about quality control and how do you make it user friendly and doable, particularly by patients? And there are all different potential requirements, maybe different quality controls for the hospital setting versus the home setting. There are liquid controls. There are electronic cartridge controls. How frequently does one need to do this?

And then there are some important clinical issues, clinical questions, about patient selection for patient self-testing, as well as patient dosing issues. So to come to a close then, I would just like to, not necessarily suggest but perhaps put up for consideration that the original derivation of a correlation between whatever the instrument is and whatever that technology is with some standard format in order to derive your mathematical equivalency, to me requires many data points, hundreds perhaps, to achieve something that is valid. To me I think one needs a wide INR range going from one up to ten or so and not just around the therapeutic range. I think that one needs to look at whole blood samples with varying hematocrits within the range of what one will typically find in patients. One needs to look at different platelet counts. One needs to look at other red cell disorders, sickle cell disease and other things; how does that influence the test?

In some instruments it may not be a factor, in others it could be. And then what is the quality of the commercial thromboplastin and instrument that it's compared to? What I would suspect at this time, what I would perhaps think most appropriate at this time is that in order to derive that initial formula, one is going to choose a good quality commercial thromboplastin and a common good recognized instrument to test your instrument against and to standardize what you have in order to derive the hundreds of patients that one might need and the different INR ranges and other things.

On the other hand, as you move down to calibration of new thromboplastin cartridge combinations, in that case I think one needs fewer data points, more restricted INR range, and, in fact, there the World Health Organization calibration scheme might be the most appropriate for calibrating new cartridges and new thromboplastins as they are produced. Thank you very much.

[Applause.]

CHAIRPERSON MICHAUD: I see a few of you fanning yourselves. I think we'll ask one of our staff to step out and see if they can adjust the room temperature accordingly. Okay. Thank you, Dr. Ansell, for your very interesting remarks. Our next speaker is Dr. George Despotis. Dr.

Despotis is an Associate Professor of Anesthesiology and Pathology at the Washington University School of Medicine. His clinical practice is divided between cardiothoracic anesthesiology and transfusion medicine and blood banking.

He is board certified in anesthesiology and board eligible in transfusion medicine. Dr. Despotis' research interests include point-of-care diagnostic testing to monitor anticoagulation reversal, point-of-care assays to optimize management of bleeding, as well as blood conservation strategies. Dr. Despotis.

DR. DESPOTIS: Good afternoon and I'd certainly like to thank Dr. Michaud for inviting me to be here with you this afternoon to address, I think, a very important topic. Over the next ten minutes, what I'd like to do in specific is address the issue of standardized assessment of accuracy of point-of-care test systems in terms of monitoring higher heparin anticoagulation.

And before starting, I'd to thank Dr. Heinrich Yost for helping me give his input on some of these slides. But as a preface to this, I'd like to say that what I'm not going to address today is the ability of these point-of-care tests to examine the issue of clinical efficacy of heparinization in terms of inhibiting or suppressing activation of the blood clotting system. With that said,

what I would like to address is the actual standardized assessment of these type of systems.

And clearly I think we have to understand what is the setting of higher states of heparin anticoagulation and that really belongs in two major categories. That is in areas where we use extra-corporal circulation, the predominant being cardiac surgery involving maybe 600,000 cases a year, but also the hemodialysis setting, and in addition the cardiac catheterization laboratory, maybe not quite as high in terms of heparin dosing and concentration, but clearly another area.

In terms of test systems specifically, and I'm going to echo some of the previous speakers on some of this, but in terms of heparin anticoagulant effect monitoring, I've listed quite a few assays for you here. I think the major one that is the most commonly used, is, of course the activated clotting time, and, I use this term loosely, but quote-unquote "the gold standard" for anticoagulation monitoring. However, there are new and emerging technologies and test systems that will be available, if not currently available, to help us with the dilemma.

And the big differentiating feature between these type of test systems and the other category, that is heparin concentration, is that with anticoagulant effect monitoring,

we're not looking just at the circulating concentration of heparin, but also its clinical effect, which may vary substantially between patients based on a number of patient and perioperative variables that can affect measurement. For instance, ATIII deficiency, we would never use a system like the automated protamine titration or heparin sensor or fluorometric assay to only monitor with those type of test systems because we would miss those patients who have substantial ATIII deficiency and that might be quite detrimental in certain scenarios.

Well, in terms of looking at standardized assessment of accuracy, the way I perceived this issue was that I think the old vantage point would be that we use some gold standard laboratory reference, and unfortunately I really don't believe that that's probably the best approach in this, and again I'm echoing a number of the statements made earlier from the previous speakers, but I think when you're looking at laboratory based methods such as plasma based anti-Xa chromogenic assays or protamine titration, although they're very nice assays, there are clear limitations. Again, these are really heparin concentration assays and so really we're not assessing some of the important properties of tests such as the ACT which look at anticoagulant effect because, as you're well aware, in the anti-Xa, for instance, we're putting back ATIII into the

system and taking that out as a variable. And that's important clinical information.

But again some of the important limitations with these type of test systems are they're not generally available in most, especially smaller-hospital based settings. Clearly, there is no standardization of these type of assays and there are a lot of--and I'm not really going to get into this--there are a lot of preanalytic and analytic variables that influence the relationship between these type of assays and the whole blood systems.

So I guess at that vantage point, what I'd like to do is propose a suggestion in terms of how we might consider at least looking at standardization of how we can look at accuracy, and really when I drafted this slide up, I thought that maybe the best approach might be the manufacturer, the burden being placed on them to look at and create a performance reference. And maybe the way I'm rethinking this maybe the manufacturer but maybe also the institution being able to generate that type of performance reference.

And what I mean by that reference is that when you're looking at a given test, you would then look at the response of whatever you're trying to examine, whether it be heparin anticoagulation or warfarin, but look at the response of that given test system in a series of normal

patients or volunteers, and then go back through time, whether you're using the manufacturer's standard or you've created an institutional standard, go back and relook at that heparin dose response, for instance, to look at the system performance over time. And again, if we're looking at heparin, that would be an example of anywhere from one to eight units per cc at normal thermia.

But as I'll show you in the next few slides, there are a number of other issues, especially with cardiac surgery, that make this story a little bit more complicated, and maybe we should be adding other issues in terms of the heparin dose response such as the system response to hypothermia, to hemodilution, or to ATIII depletion, for instance. So to address this a little bit more adequately, I'm going to spend the next few slides looking at these particular issues and then reiterate this proposal.

This is some data that we've generated from our institution in which it was basically an in vitro study. We obtained blood specimens for about 32 cardiac surgical patients and then we spiked those blood specimens with known amounts of heparin and, of course, this is the linear relationship between in this case the kaolin ACT based on the Medtronic platform as it related to whole blood heparin concentration. And again, if you look generally at that relationship, you see that it is a nice linear relationship

if you plot the mean values over that range of concentrations.

However, you can also see there's quite a bit of variability. Those are standard deviation bars illustrating that there is quite a bit of variability and confirmed by that R value of 0.79. And of course, that would be a little concerning, but as we're well aware, as you see with most PT and aPTT reagent systems, the response can vary between patients. And in this setting, we not only have plasma issues but we have cellular components such as platelets and red cells that might be influencing our test result.

If you actually look at the correlation among patients, then you actually, if you average those correlation coefficients, they average to about .98, and to illustrate this concept further, that's what we did. We examined the individual relationships in those 40 odd patients, and you can see here, and this is just an overview, but you can see that, in general, there's a fairly nice linear relationship between ACT values and heparin concentrations.

Now, it might become log linear, for instance, in the upper left corner, an increased responsiveness, or if you can see in the middle of the slide, there's one patient that has a log linear decreased responsiveness to heparin

with concentration, but in general there is a very nice linear relationship so that standard deviation we saw on the previous slide, it was really related to patient related differences. And so that is something to keep in mind when we're thinking about standardized assessment of these assays.

In addition, there are other confounding variables that can occur in clinical scenario. The same type of analysis, except now we're looking at ex vivo in a series of 32 patients undergoing cardiac surgery and cardiopulmonary bypass. Again, the relationship of kaolin ACT to anti-Xa heparin assay from Dr. Yost's lab, and you can see here the R-squared is 0.58 and a lot of scatter. Some patients with an ACT of 400 seconds had lower than one unit per cc, whereas other patients had eight units per cc of heparin at that ACT value, and so indicating that in certain clinical scenarios, there might be a lot of effects of perioperative factors that can influence these test results.

What are some of those factors? Well, in our setting in cardiac surgery, another study we published looking at some of these factors, again a series of 32 patients, we're looking, the yellow at the top is celite ACT, the blue is kaolin ACT, and we also used an anti-Xa in white and a whole blood, the automated protamine titration--in purple--assay to look at heparin concentration. And the

common points here from the first point to point A is heparinization and clearly there's a rise in both heparin levels and ACT values.

But the real divergence occurs when we initiate cardiopulmonary bypass at which time you can see what happens to heparin levels. They plummet at a time where ACT values either stay the same or increase. And the reason why that divergence occurs is two part. First, heparin levels drop because of the time interval there, about 45 minutes, but also because of the hematocrit, the amount of hemodilution that occurs with the initiation of bypass.

In any event, clearly if a clinician wanted to maintain five units per cc, and based it off the initial ACT value, that you could see how they would be misled, and, of course, this is important information from the clinician's perspective but again helps one understand that there are a lot of confounding factors that make standardized assessment more difficult. And, of course, that's why I'm suggesting we include issues like hemodilution and hypothermia when we're assessing the effects of these variables on particular assay systems.

Finally, again, another study that we published looking at the responsiveness of a couple of these test systems, celite in yellow and kaolin in blue, as it related

to ATIII concentration. We obtained specimens from volunteers, approximately ten, reconstituted platelet poor plasma with ATIII deficient plasma, and then generated these response curves. And as you can see, when you get below about 80 to 100 percent activity on ATIII, there is a nice linear relationship that has reduced responsiveness of these assay systems. And, of course, again, this is important information for us as clinicians when we determine what is the therapeutic dose of heparin in any given patient.

So to go back to my original suggestion, I think again my proposal would be that we generate or we allow the manufacturer to create the template for their particular given instrument and reagent system and that we allow them to prepare for us a standard dose response relationship in a large series of volunteers and, of course, that would be the white line there. Over a given heparin concentration range, what is the response of the ACT for that particular test system? We might also consider having them generate curves as above, that is the effects of hemodilution, known amounts of hemodilution, and hypothermia. And the one that I haven't drawn in there is if we vary ATIII concentration, that slope would drop.

And then we can use that as a template to know at any given time when we're using the instrument, if we want to run a small series of patients and look at that accuracy

and see if it conforms to what happens at the manufacturer's site. Again, the alternative to this would be that each institution would generate these kind of curves and then over time be able to use these to look at the assessment of the performance of these assay systems. Thank you.

[Applause.]

CHAIRPERSON MICHAUD: Thank you, Dr. Despotis. Our next speaker is Dr. Leon Poller. Dr. Poller is an honorary professor of the University of Manchester. He is a founding organizer of the UK National External Quality Assessment Scheme in Blood Coagulation and also of the WHO International External Quality Assessment Scheme in Blood Coagulation. He has been the project director of the European Concerted Action on Anticoagulation of the European Union since 1994. Professor Poller has contributed to over 300 articles in professional journals and is the editor of the Recent Advancement in Blood Coagulation series. Welcome, Professor Poller.

DR. POLLER: Thank you, Dr. Michaud, for that kind invitation for the meeting. It's good to see so many friends and colleagues here and meet them again. The first slide, please. Normalization and Standardization of Home Prothrombin Time Monitors is a program of the European Commission of the European Community Steering Group which

has just been--Dr. Michaud, Dr. van den Besselaar, Tripodi, van de Meer, and Preston, our consultant.

We also have national control directors--next slide, please--in each of the 16 EU member states and many of these names are very familiar to you. We all share the interest in the home monitors and the effort to bring them into the WHO scheme.

The next slide, please. The aims of the European Concerted Action on Anticoagulation have been to improve the laboratory control of oral anticoagulation and improve dose regulation which is [?] medical program and the present topic, normalization and standardization of home prothrombin time monitors on the standards, testing and measurement program.

Traditionally, tests used for the control of oral anticoagulant treatment, as you all know, have been plasma methods, but recently the usage of oral anticoagulant treatment has expanded enormously and in response to this a new system of home testing PT monitors based on testing an unmeasured whole blood sample has been developed. This is, of course, a revolutionary approach offering potential great advantages. Up till now, all laboratory methods for anticoagulant control have been dependent on skilled laboratory personnel. Home prothrombin time monitors offer the testing by relatively unskilled personnel including

indeed patients themselves, thus avoiding the need for hospital or clinic attendants.

Manufacturers employ quality control procedures to attempt to conform to WHO guidelines, but there is no possibility of calibrating all instruments in accordance with PT standardization WHO scheme. Without adequate calibration to accord with the WHO scheme, widespread introduction of the monitors resulting from consumer demand would in the views of many of us result in a return to the unregulated state of oral anticoagulant control which existed before the introduction of the WHO scheme.

The only valid way--I expected howls of protest at that remark--but the only valid way to calibrate the home monitors was proposed by Tripodi in his publications. Next slide, please. And the development--next slide, please--the parallel calibration of unmeasured whole blood samples on the home monitor combined with conventional PT manual testing using a thromboplastin IRP on the plasma samples from the same subjects collected simultaneously as the whole blood samples.

An example of one of these calibrations is given in then next slide taken from Tripodi's paper which shows the calibration of a monitor in terms of the EC reference thromboplastin for rabbit, CRM 149R [?], the tests on the 20

normals and the 60 coumarin samples on the log-log plot, the regression analysis giving the slope and from this the ISI derived. This is a very laborious process totally impractical for the calibration of individual monitors apart from very interested parties such as manufacturers doing the main batches.

The aims of the ECA project therefore is to develop a simpler system which can be used widely and with confidence by manufacturers and others and to give a calibration and also to provide quality control material. I'll come to that later. There are big problems with the WHO scheme in respect to the monitors. Next slide, please.

Conventional WHO calibration requirements are very considerable. You have to have skilled personnel conversant with the manual prothrombin time technique, obviously not practical for the usual home monitor user. You have to have a supply of 20 normals, plasma from 20 normals, and 60 patients on anticoagulation, which is quite a task to collect. You have to have the local supply of the thromboplastin IRP, which is usually very difficult to obtain, and really one would say you have to have a multi-center calibration because a single calibration doesn't carry a great deal of weight.

So there are enormous problems if you say you should do a WHO calibration, the conventional one on the

home prothrombin time monitors. Then again it's accentuated by the massive numbers of monitors. You're going to be dealing with thousands as opposed to the few, one or two in the laboratory, perhaps a thousand or so, the equivalent one per patient. There are the different types of monitors using different types of end-points and different test strips even with the same monitors, all of which need calibrating.

And some monitors, we found to our cost and travail, do not provide results in real seconds. They are virtual seconds. So you can't really do a WHO calibration without some very complex conversion. So these are some problems in the WHO scheme.

And then on this next slide, monitors have particular problems. Using whole blood, un-citrated whole blood, you're comparing with citrated plasma controls and this has to be carefully regulated. They have red cells in the testing. Do you need a substitute? Red cells alter the test volume and also have a mechanical effect on the testing. If you're going to use lyophilized plasma for controlling, how do these lyophilized changes affect the monitors? And again you get different types of end-points with the monitors. Some have a simple clotting end-point.

Some have aggregation end-point. Some have all sorts of mechanical end-points that I don't totally understand.

So there are problems with the WHO calibration system as it stands for monitoring the convention. Well, how are we tackling them in the ECA program? Next slide, please. First of all, we are doing some--this is a plan--preliminary investigations on the effect of citrate anticoagulant, the effects of lyophilization at a few selected laboratories. We will endeavor to produce a protocol for the calibrant in quality control plasma for the preparation, to prepare pilot batches, certify these in the appropriate ways with the role of an IRP for thromboplastin.

Then we come to our major undertaking which is a large multi-center calibration study at the ECA national control laboratory. This will be the test of whether the WHO simplified system compares with the full conventional WHO system because that's what they'll be doing as well. They will be doing the Tripodi type testing. And also an indication of the inter-instrument variability of instruments of the same type and whether they conform to the criteria.

The analysis of the calibration, the study and their recommendations will be our last endeavor. Next slide, please. We also have to tackle the question of quality control to ensure continuing conformity to the WHO

standard by regular checks of inter-instrument variation, to check into batch variation, test strips and cartridges, and to check performances of operators.

And finally, there are the outcomes which--the next slide, please--last slide--we hope will be the development of a simplified calibration scheme for home PT monitors to allow them to accord to the WHO system. This will be on the basis of the multi-center study. We will be able to assess inter-instrument variability by calibration and quality control. We'll be able by ongoing quality to ensure continuing uniformity and the end result will be conformity to WHO standardization. Finally, I'd like to thank the manufacturers who are cooperating with us in this project. Thank you.

[Applause.]

CHAIRPERSON MICHAUD: Thank you, Professor Poller. Our final panel will be representing the viewpoints of the proficiency testing, regulatory and standards development organizations. Dr. John Brandt, our first speaker on the panel, is speaking for the College of American Pathologists. Dr. Brandt is currently a senior clinical research pathologist with Eli Lilly and Company in Indianapolis, Indiana. Prior to joining Lilly in January 1999, Dr. Brandt was a professor of pathology at the Ohio State University in

Columbus, Ohio, where he was Director of the Hematopathology Program.

Dr. Brandt has served on the Coagulation Resource Committee of the College of American Pathologists since 1984 and served as chair of this committee from 1993 to 1998. He is also currently a member of the Standards Committee of the College of American Pathologists. Dr. Brandt.

DR. BRANDT: Thank you, Dr. Michaud. It is a pleasure to see many friends who have wrestled with this problem for a number of years. Sometimes I think it's like getting into a pigpen and we all come out with a little mud on us. The stories are starting to sound a little similar and I think as I go through my talk, you'll pick up several themes that you've heard from the previous speakers, and indeed I think we might be starting to get our hands on this problem.

If you think about the concept of standardization itself, it really implies that the methods and devices used to perform those measure the same thing. An example would be blood glucose and the whole blood glucose analyzer, finger stick analyzer ought to correlate with another chemistry analyzer for glucose. The problem that we face, and there are several problems, in terms of the coagulation assays are that coagulation is in general measure a complex multi-component process, not a single analyte.

As has been pointed out, it is likely, it is definite that the process which occurs in whole blood is very different, fundamentally different, than the process that occurs in plasma. Okay. So we're talking about different processes. In addition for any given process, if you want to call it an ACT or a PT, differences in the reagent composition or the device function may also affect the process that occurs so that an ACT performed with one set of reagents, as we've already seen this afternoon, may not really be the same process as that performed with another set of reagents.

Another component is that biologic variation also affects the process. And Dr. Despotis showed us some slides that point this out very well. Basically in a different individual, the process will be different. So how are we going to truly standardize all these different processes?

I think it's going to be difficult--some would translate that to impossible--to achieve what we would call true standardization. That is that you have a definite reference point that everything will give you a common answer to. We are actually using different processes to tell us something about the hemostatic system.

Well, does that mean we get up and take a break and go home, end of story? I don't think so. I think we're

starting to hear that there are things that can be done. As Dr. Ansell pointed out, really what we're interested in is the clinical endpoint: do these procedures give us relevant clinical information? Do tests of the same name, ACT, that are trying to measure anticoagulant effect in cardiopulmonary bypass provide equivalent clinical information? Does the whole blood PT provide the same clinical information as a plasma-based PT? And that really, I think, ought to be our focus.

How do you get there? There are some focus points, I think, that we can start to hone in on. One is under the rubric of calibration. This really is a matter of determining the functional characteristics of the assay system dose-response relationship. It could be the heparin to oral anticoagulant effect, to the level of Factor V, to the presence of the lupus anticoagulants, some measure of the dose-response characteristics of the individual system. This needs to be defined for each particular system as well as possible.

Then there needs to be some type of validation where the system is assessed under clinical conditions. Often this will require simultaneous testing with a previously validated system or comparison to clinical outcomes or some combination thereof. So with the validation, you're basically asking does this particular

test provide the information that we think it does? And is the response characteristic?

And then finally I think we can talk about harmonization and really gets to Dr. Ansell's question is does this procedure provide equivalent clinical information to that provided by another test system? With this, there may well be reference test systems that are maintained somewhere that can be used for comparability, but I don't know that we can ever call them the gold standard. They may simply be a reference point to which we may be able to link things. So a couple of thoughts in terms of standardization.

Now, how does this all relate to proficiency testing and what's the role of inter-laboratory proficiency testing? Inter-laboratory proficiency testing can provide some useful information on laboratories using the same method. It gets a little dicier when you're talking about different methods. Inter-laboratory proficiency testing can provide some information on calibration. We can have samples spiked with a given level of heparin and get some estimate of a particular test system response to that level of heparin.

We can through the questions and interpretation of the data that an individual laboratory derives from the

tests that's performed get some information regarding harmonization or the interpretation. Is this answer therapeutic? Is this value therapeutic or is this not therapeutic, for example? But there are also some limits for proficiency testing. It is certainly not going to be the end-point solution here. There are real problems with designing the appropriate test samples, for example.

At the college, we've thought about, we've scratched our heads, but we really have not come up with a way of having a sample that could be used to test both plasma and whole blood instruments simultaneously. I mean in an ideal world, it would be great to be able to do that. In practical terms, we haven't been able to do it.

The term "matrix effects," this is a sin that covers a lot of errors. But it is real. You can take a sample and for some reason the composition of that sample, whether it's a buffer that's in there or whatever, has an interaction with a particular reagent instrument combination, and if you're then trying to legitimately compare the clinical performance of those instruments, that matrix effect will really compromise that interpretation.

And then there are also the challenges of coming up with appropriate samples. One example is coming up with a truly high heparin concentration in an ACT based survey. Technically, it's been very difficult to do that. So there

are all sorts of problems with the appropriate test samples. And then also just the design of the program. And here some of the near-patient testing adds to the level of complexity.

For example, at any given institution, there may be multiple instruments. Take glucometers. How many glucometers are there in your hospital? How many coagulation, bedside coagulation instruments are in your hospital? Does each one of those participate in a survey? Or do you have a certain number, a subset of those, participate in a survey? How is that done? The second problem is that there are often multiple uses for a given test throughout the institution, and here the ACT is a good example because the clinical decision point may vary depending on the site where that instrument is used.

For example, on the ACT surveys for the CAP, we ask basically where is the instrument being used? Here is the distribution. About a third in the cardiac cath lab, 23 percent cardiopulmonary bypass, about nine percent hemodialysis, intensive care unit, 19.1 percent, and then scattered all over the place. We also sent out a sample, and the testing was done by a variety of sites in the hospitals. We asked them to judge was the result below therapeutic, therapeutic, or above therapeutic. If you're in the cardiac cath lab, about 71 percent were above

therapeutic; cardiopulmonary bypass, only 24 percent. In your dialysis unit, 100 percent were above the therapeutic range.

So, you know, what's the real clinical information being given here? I think we have to keep this in mind as well as we try and develop the clinical correlation for given methodologies. Something may well be validated for performance in cardiopulmonary bypass. That doesn't mean it will automatically be validated for hemodialysis until you actually have the data in hand.

Finally, proficiency testing is not a substitute for robust quality control processes. I know in the near-patient/self-patient testing arena, this can be problematic, but the experiences of most people who have worked in laboratories over a period of time is that instruments and processes fail. And if you don't have a system available to detect failure of your basic system, all the standardization in the world is not going to protect the patient. So this has got to be a part of the program.

In summary, true standardization of coagulation assays has been limited really, I think, because the assays measure a process, not a distinct analyte. And I think we've tried to force everything into a square two by two and they aren't all squares that are two by two. Proficiency testing can be helpful in assessing calibration and

harmonization, but there are real limitations to the ability of proficiency schemes in order to verify that the systems are truly working. Thank you.

[Applause.]

CHAIRPERSON MICHAUD: Thank you, Dr. Brandt. Our next speaker is Dr. Steve Gutman. He is representing the U.S. Food and Drug Administration on our panel. Dr. Gutman is a board certified pathologist with a medical degree from Cornell University Medical College and an MBA from the State University of New York at Buffalo. He completed residency training in anatomic pathology at the New York Hospital and also trained in clinical pathology at the Mayo Clinic.

After ten years of experience as a clinical pathologist and Chief of the Laboratory Service at the Buffalo Veterans Administration Medical Center, he joined the Division of Clinical Laboratory Devices in February of 1992 where he now serves as division director. Dr. Gutman.

DR. GUTMAN: Good afternoon. I want to thank Dr. Michaud for, at least for this session, putting me last. The FDA always likes to have the last word and I'd actually also like to thank her for taking the lead in our division for putting together this effort. And Dr. Michaud has given me the assignment of concisely and precisely trying to

provide you an overview of what we do and why this enterprise is so important to us.

Regulation of in vitro diagnostic devices, also referred to as IVDs or lab tests, like all medical devices, was first put into place in 1976 with the passage of the Medical Device Amendments. This new law established for the first time in the United States a variety of controls for medical devices including two key new requirements: the requirement that new products be subject to premarket review by FDA before be putting into the commercial medical marketplace and the requirement that medical devices be made according to good manufacturing practices, also referred to as GMPs.

Premarket review of IVDs is focused on understanding the basic performance characteristics required to assure their safe and effective use. For all products, this includes an elucidation of their accuracy or bias, their precision or repeatability, and when appropriate their analytical specificity and sensitivity. Although in many cases, an analytical characterization of an IVD will suffice in supporting a premarket clearance, in some cases, the link between analytical performance and intended use is not well bridged, and in these instances, FDA review requires information on clinical or diagnostic sensitivity, clinical

or diagnostic specificity, and information on expected values in various states of health and disease.

In vitro diagnostic devices are unique among medical devices in having their own labeling regulations. These are outlined in 809.10 of the Code of Federal Regulations and include 15 sections necessary for labeling of diagnostic products and key among these is a section dictating the need for an assessment of relevant performance.

Over the course of the past 20 years of regulation, premarket review has changed significantly from a largely descriptive to a largely data driven process. And this, in part, has been made possible by evolving review experience and in part by the development of an improved science for evaluation including an emerging literature base and the promulgation of a variety of guidances, guidelines and voluntary standards.

FDA oversight of good manufacturing practices was initiated also in 1976 to ensure that sponsors produce devices with sustained performance which maintain conformity with their labeling and met user needs over time.

Next slide. The program in many ways is for industry the moral equivalent of the CLIA oversight program for laboratories. Key components of GMP include

requirements for controlled environment appropriate to production of the device, for appropriate training of personnel involved in production of the device, and for ensuring that mechanisms for monitoring control of the production process are in place.

In 1997, major changes were made in this system and these changes were improvements and upgrades in the GMP system as a result of modifications in the regulations actually outlined in the Code of Federal Regulations. And the new process put into place was referred to as the quality system regulations, or QSRs, and the QSRs had two important features. One was a deliberate effort to harmonize U.S. requirements with manufacturing requirements developed in Europe, and the second was the utilization of modern concepts of quality management in production programs.

In addition, a unique feature of the QSRs was introduction for all Class II and Class III, relatively higher risk devices, and for selected Class I devices of a new requirement for design controls, which was an effort to build quality into the design of a device. And under design control, sponsors are required to identify outputs for their medical device--for an IVD that's obviously the diagnostic information it produces--to consider the inputs being used

in production of those outputs, and to assure that there is a link or conformance between these two arms of production.

Whole blood coagulation devices present a particular challenge to our regulatory oversight program in both the areas of premarket review and in the oversight of quality system regulations. And this is because of the facts you've already heard today. You probably already knew before you came to this conference that for many, perhaps for most, methodologies, there is a lack of definitive testing methods, a lack of stable reference or calibration materials, a lack of uniform methodologies for dealing with matrix issues, and no well defined yardstick for assessing acceptable levels of performance. As a result of these shortcomings, manufacturers, regulators and users all find the characterization of performance for these devices anything but a clear path.

FDA is an enthusiastic cosponsor of today's workshop in part because we recognize the substantial need to improve the scientific base being applied to whole blood coagulation devices. Whether the outcome of this effort leads to new scientific literature, to written or educational guidance materials, or to voluntary or for that matter to mandatory standards, there is considerable room for improvement and need for better science.

Although the agency has always been anxious to work with outside groups to develop guidances and to help foster voluntary standards, as a result of the reengineering program being applied to devices, there is real added value to this type of enterprise. Under the new regulatory paradigm being applied to new versions of old coagulation devices, it is now possible for the agency to formally recognize standards and to utilize conformance to standards as a surrogate for all or appropriate selected subparts of premarket review.

The result of this pragmatic change is a tremendous incentive to us and to industry and hopefully to professional groups as well to develop well conceived and constructed standards to frame the science and to allow for a clear, straight and hopefully simple path to premarket clearance.

Next please. The product of this workshop and of subsequent efforts to deal with the issues being addressed today can only do general good by improving our ability to understand this area of testing. An added, rather specific reward to both sponsors, the agency and the medical marketplace is the possible opportunity for a faster route for better products to enter the marketplace.

For FDA that is the bottom line. Our agency has a distinctive dual mission to promote the rapid entry of good

products into the marketplace while hampering or preventing bad products. We believe passionately that good science is the key to this mission. We view today's enterprise as a starting point in an ongoing dialogue to be applied to a wide variety of hematology products and we look forward to working with both industry and professional groups to using this dialogue as a tool to promote both personal and public health.

[Applause.]

CHAIRPERSON MICHAUD: Thank you, Dr. Gutman. Although Dr. Gutman was hoping to have the last word and at the risk of disappointing him, that honor, in fact, goes to Dr. Anton van den Besselaar. We are very pleased that Dr. van den Besselaar accepted our invitation to present his views based on many years of experience in standards development.

Dr. van den Besselaar is deputy director of the Netherlands Reference Institute for Laboratory Control of Anticoagulant Therapy. He graduated from the University of Utrecht where he received a Ph.D. in biochemistry. He chaired the ISTH Scientific Subcommittee on Control of Anticoagulation from 1986 to 1989 and he presently cochairs this subcommittee. He was involved in the establishment of several international reference preparations for

thromboplastin and in particular the WHO and the European Community's reference preparations. Welcome, Dr. van den Besselaar.

DR. van den BESSELAAR: Thank you, Dr. Michaud, for inviting me. Ladies and gentlemen, I realize that I'm the only non-native English speaker this afternoon. So please be patient with me. I would like to present to you some aspects of the document that was originally presented or published in 1983 and this document which was published by the WHO Expert Committee on Biological Standardization was entitled "Requirements for Thromboplastins and Plasma Used to Control Oral Anticoagulant Therapy."

This document was revised in October in 1997, but unfortunately it's not yet published although it is available from the WHO. We hope that it will be published really soon so that everybody can read it. The document, the revised document, starts with definitions of all the terms that are used in standardization and calibration. So we have definitions of tissue factor, thromboplastin, prothrombin time, prothrombin time rate system, mean normal prothrombin time, prothrombin time ratio, international sensitivity index and international normalized ratio.

And it's the INR which is important to us. I'm sorry about this slide. I hope you can read it. This is a diagram of the relationships between WHO international

reference preparations that are used to calibrate thromboplastins, commercial thromboplastins and national thromboplastins. At the top of the hierarchy, we have the first international reference preparation which defines the INR scale and had an ISI of 1.0 by definition. And all the later generations of international reference preparations were calibrated against this first preparation in multi-center calibration studies.

Today, we have three international reference preparations. One from bovine thromboplastin. It's named OBT 79. We have an international reference preparation for human thromboplastin, human recombinant, and the third is an IRP for rabbit thromboplastin. Now you may wonder why do we need three IRPs, one would be sufficient, you might think. Well, this is because previous studies have shown that the correlation between thromboplastins of the same type or the same tissue are better than correlations between preparations from different tissues. So the calibration, the precision of calibration is better when you have a like to like comparison and that is the reason why we have three IRPs, one for each species.

Furthermore, the availability of three international reference preparations allows us to monitor the long-term stability of the IRPs because they are

biological materials and in theory they could deteriorate over time and therefore we can interrelate the three IRPs and in this way ascertain or assess their stability.

Now, there are four types of PT system calibration. The first is calibration of international reference preparations. I will not discuss this further. But the second type of calibration is the calibration of secondary reference materials or manufacturers' in-house standards. And this is a very important step in the calibration sequence because this is what manufacturers should do when they calibrate their reagents against the WHO materials.

The third step is the calibration of subsequent lots of a certain type of commercial thromboplastin against the in-house standard. This is also called lot to lot calibration. And the fourth type of calibration is the calibration of local PT systems. Now, you should realize that there is variability in ISI calibration. So when you determine ISIs in different laboratories according to the same protocol, you still have variation. And in order to minimize this variation, it is recommended that the calibration of a manufacturer's in-house standard should be carried out by at least two laboratories and the more laboratories you have, the less you could minimize the error in the mean ISI.

Now this is the procedure that is used or is recommended for in-house standard calibration against an IRP. This should be done on at least five separate occasions or days. On each occasion, you need fresh reagents and fresh blood samples from healthy subjects and patients who have been on oral anticoagulants for at least six weeks. The total number of healthy subjects should be 20 and the total number of coumarin patients 60. And the same person should perform the PT tests because with the IRP it's always manual technique. The statistical evaluation of the results or the data should be that the samples should be within the therapeutic range. So only samples with INR between 1.5 and 4.5 should be used for the calibration because the INR is really defined only for the therapeutic range.

So an INR of ten has very little meaning. The log PT with a reference system is plotted on the vertical axis and the log PT with the test system on the horizontal axis and you should check whether there is a single regression line going through the patient samples and the normals.

Samples with a greater distance than three standard deviations from the line should be excluded and the coefficient of variation of the slope of the line should be not greater than three percent. Then when this is done, we

have the lot to lot calibration and this can be done with a fewer number of samples because in general the lots are very similar so the variation above the line is smaller and you could use a smaller number of samples. But at least a pool of normal plasma and at least two pooled coumarin plasmas or at least two artificially depleted plasmas should be used. Samples should be freeze-dried or frozen. We need at least four separate occasions, fresh reagents on each occasion, and the whole procedure should be validated against a fresh plasma or fresh blood procedure so procedure one.

Well, the document ends with the following remarks. All medical staff should be encouraged to use the INR. The INR system can be accurate only in the range explored by the calibration procedure. That is stable oral anticoagulation with INR between 1.5 and 4.5. Manufacturers of commercial reagents should state on the package insert the ISI of the relevant batch of thromboplastin together with a reference preparation against which it has been determined an instrument for which it is valid.

Now I don't know--how much time do I have--okay. Well, maybe I skip a few slides. Perhaps I should discuss this one. The manufacturer's calibration of whole blood PT devices should follow the procedure one that I just discussed. So there should be a calibration of a house standard cartridge. Conventional ISI calibration with fresh

samples against the international reference preparation should be done. And these should be plasma samples. We need 20 normals and 60 patients. We need at least two centers. Lot to lot calibration can be done with fresh, may be done with fresh frozen or lyophilized samples. There is little experience with this so this should be investigated. And we should realize that the manufacturer's calibration is stored in the device's memory. So it is unlike the traditional PT test where you get an ISI in the box insert. Here the whole calibration is already stored in the instrument itself. So it's difficult for the user to check the calibration.

Well, okay, we can skip this one, skip this one. Well, you could check the calibration of a whole blood PT device. You should again realize that the manufacturer's calibration is stored in the device and the device displays results either clotting times or INR directly. At this moment, the user cannot change the manufacturer's calibration and the question is, of course, is local calibration by the user required?

So the calibration should be checked in some way. Now, I think maybe I'll show one slide where I give the idea. Here we compared INRs obtained with two different lots of a certain type of whole blood device which is the

Coaguchek instrument, and you can see that there is very good correlation between the INRs with the two lots and also the variability around the line is fairly small, but, of course, we have to compare the INRs with the device to INRs with an IRP and this is shown in this slide.

On a vertical axis, the IRP, the INRs with the device, and the horizontal axis, the INRs with the international reference preparation. And you can see there is a good correlation, but there is a slight bias. The diagonal is the line of identity, the Y equals X relationship, and you can see that the device underestimates the INR to a small extent, but if this is smaller than, let's say, ten percent, I would say this is acceptable. But this is, in general, the way in which we can check the calibration of a whole blood PT device. Thank you.

[Applause.]

CHAIRPERSON MICHAUD: Thank you and thank you to all our speakers for their very insightful and I think thought provoking comments this afternoon. We won't be entertaining questions and comments from the assembly at this point in the workshop. Rather we'd like to stop here and take a short break before dispersing into the small discussion groups. That begins, the discussion group meetings start in ten minutes at 3:15.

We want you to know that food and beverages will be available in each of the meeting rooms. Also, the rest rooms and phone banks are in the area immediately adjacent to the registration desk for your information. I want you to know that each one of the participants has been assigned to a specific discussion group. We took individuals from each sector of activity, whether it be end-users or industry or proficiency testing organizations, and we randomly assigned them to each one of the discussion groups with the intention of having balanced representation in each of the groups.

Your package also contains a brief outline of the tasks that we're hoping you will accomplish and we're hoping that this will give you some focus for the work that needs to be completed in the very short time that you have. We recommend that you designate a reporter for your session very soon after you begin because this individual's responsibility will be not only to convey the results of your deliberations to the assembly once you return to the plenary session, but we're also asking that the reporter keep the group on track as much as possible in terms of the tasks that we've assigned to you.

And so we'll ask you to go to the small breakout sessions by 3:15. I believe we also have beverages just

outside the door. Pardon me. I made a mistake in telling you that your assignments were in your folder. In fact, if you go to the registration table, we will be telling you exactly which room you're assigned to. Thank you.

[Whereupon, following a short break, participants met in assigned break-out groups from 3:15 p.m. to 4:40 p.m., upon which conclusion, the plenary session was reconvened.]

CHAIRPERSON MICHAUD: We ask you to please take your seats so that we can begin this afternoon's program. I'd like to ask everyone to please take their seats. We'd like to get started, please. Thank you. I'd like to ask Dr. Douglas Triplett to come up to the stage. He'll be moderating this afternoon's or this final plenary session. We'd also like to have the reporters from each of the break-out sessions, we'd like to have them come up to the stage so that they can be available to present the results of their deliberations.

DR. TRIPLETT: I guess the agenda is we'll start with Group Five and go back toward one. So those of you who had five and thought you were off the hook, you're going to start first. So can we have the group and the spokesperson or spokespeople for that group?

MS. STUART: Okay. For the first task, we decided that we might have greater than one project going here and

that obviously PT would be easier and we thought that we would try to develop a global standardization procedure for all plasma and whole blood coagulation systems. In addition, we'd like to develop a global standardization procedure for all plasma and whole blood coagulation systems which will ensure the consistency of patient treatment from system to system and site to site.

For the second task, we've decided that we would like to look at the present and future whole blood hemostasis assays across the defined clinical applications for each test.

And the third task, we would like to define a clinical standard and develop acceptance criteria such as precision and accuracy. And that's it for Group Five.

[Applause.]

DR. TRIPLETT: Those are lofty goals. John, would you care to comment about the discussion that occurred?

MR. OLSON: In our group?

DR. TRIPLETT: In your group.

MR. OLSON: Sure. I will. I was in Group Four. Are you ready to move on to the next group?

DR. TRIPLETT: Okay. You're in Group Four.

MR. OLSON: I am.

DR. TRIPLETT: Okay. We need a Group Five representative. Does anyone want to amplify on those discussions or topics that were outlined?

PARTICIPANT: Do you want someone from the group?

DR. TRIPLETT: Yes. Does anyone want to amplify on what was outlined or are there questions from the audience to the group?

PARTICIPANT: The only other aspect was in trying to get this done, we'd like to see it done globally and in addition therefore we'd like to have the same clinical outcomes with the same patient. And obviously we would have to address or define all clinical applications in order to get to the scope of the project.

And for the third task, the additional comment is that we would primarily address the primary intended use for POC whole blood testing and for aPTT and whole blood setting. Therefore, we would need to establish a normal baseline and other types of criteria.

PARTICIPANT: And one other thing we talked about was that perhaps the word "standardization" isn't really appropriate, that the term that was used in earlier presentations, that "harmonization" might really be a more appropriate definition in this case. You don't really have already defined standards. Perhaps harmonization is the best you can hope for for the time being.

DR. TRIPLETT: I would agree with that. There's a comment?

PARTICIPANT: The only thing that I also wanted to add is that when we talked about standards, we said clinical standard which didn't mean a standard in a bottle. That we were looking at, you know, what was really defined as the clinical and what the use of the test would be. So looking at the clinical applications of the test.

DR. TRIPLETT: Okay. Any other comments?

PARTICIPANT: I have one more, Dr. Triplett.

DR. TRIPLETT: Yes, please.

PARTICIPANT: I also think that we should move away from the coagulation term and move toward the hemostasis term. Looking ahead, for the future, I'm sure we'll be looking at tests for the fibrinolytic pathway so I think we should start referring to this as hemostasis test.

DR. TRIPLETT: Good point. I guess we'll go to Group Four then.

MR. OLSON: Is that the logic that we were going to use?

DR. TRIPLETT: Uh-huh.

MR. OLSON: I'm not going to use any visual aides. Our group focused the majority of its discussion on the prothrombin time and oral anticoagulant monitoring. But I

think some of the ideas we have can be expanded into the other tests that have been discussed here. So in relation to the aims, I think we focused our thinking there about this problem of what is a standard. And the comment that was made earlier that the standard isn't necessarily what's in the bottle, but may actually be the outcome or a relationship to an outcome.

And in relation to that, we would agree with what was brought out by Group Number Five, and that's that testing with these kinds of devices really need to be focused around the clinical application to which they're being applied. That's an easy thing in relation to the PT INR because virtually all the testing that's being done with these whole blood devices is for oral anticoagulant monitoring. So there's already the focus present there. It's less easy to define in relation to ACTs and PTTs and so our thoughts were let's start doing something along the lines of the PT INR and maybe the things we learn there can be applied in other clinical settings.

So the task two in terms of the scope, our thoughts were that there is a lot of leg work that's already been done with the PT INR and that working in that arena in terms of defining methods for standardization and moving these things to the point of care may be easier for the regulators that have a concern here.

The elements of this are kind of threefold as we discussed them. We have 60 years worth of experience with plasma prothrombin time and it can't be discarded. However, I think that a number of people have brought out the idea that the whole blood test may not be exactly the same thing as the plasma test.

I like the definition of paradigm that states that a paradigm are the boundaries that limit your thinking and I think we are in a plasma paradigm and we are forcing ourselves to relate everything back to our knowledge related to plasma coagulation. So I think there may be some value in not abandoning that but of collecting the information about what the real clotting times are in these devices. And we may find that there is a better way to do this. There is an awful lot of testing that's being done, and if we actually knew what the measurements really were, we may learn something from them.

The second point is that we would like to see as much of the standardization or calibration process be in the hands of the manufacturer as possible. You know in What Cheer, Iowa and Del Rio, Texas, it's going to be very difficult to do complicated things and that's where the patients are. Even the laboratories that are located in

communities of that size are going to have a very difficult time participating in an aggressive calibration process.

So I think we really do need to try and push this process as far centrally as possible so the ideas of having whatever we define as the calibrator be readily available to manufacturers and that manufacturers develop devices and methods, cartridges, that meet certain criteria so that by the time they get to the hands of the user, whether that be a laboratory or a patient, that the only thing that they would need to worry about is the control of the device, that they can demonstrate that the device is actually working at the time that they're doing the test.

And I guess that's pretty much the conclusions that we drew. The other point, and it kind of came up as we were closing, is the role of proficiency testing in this process. There at least were some in our group that felt there was a need for a reality check, that there is, of course, a device and you're going to make measurements of prothrombin times or of INRs using that device. The manufacturer is going to tell you that the INR is going to come out a certain way with a certain thing with a certain specimen and the question is whether there needs to be a reality check in terms of some kind of testing at the point of known specimens. That's going to be a more problematic

issue and I'll close there. Anybody that was in the group can now correct everything that I said.

DR. TRIPLETT: Any comments?

MR. HILL: How about from outside the group?

DR. TRIPLETT: Sure. Anywhere.

MR. OLSON: Oh, absolutely.

MR. HILL: James Hill, Roche Diagnostics. You mentioned that the whole blood is probably a bit different than the plasma and I've heard this before on a couple of occasions. That may be true and it really would be true if I was allowed to develop the chemistry so that it really would be different and hopefully it would be superior in its ability to actually reflect more accurately the physiological status of the patient.

But I'm forced to mimic a plasma PT or aPTT, therefore, I make sure the platelets do not participate, the interleaflet phospholipid membrane of the red cells do not participate, so therefore I've never looked at the whole blood PT as being different because I'm forced to develop it to be essentially equivalent, but hopefully in the future as we become more open-minded and we're looking at these tests as a better way to manage patients or understanding the physiological status of the patient, maybe we will be allowed to develop some unique new chemistries which will

allow the cellular components to contribute to the clotting. It may not happen in my lifetime or I may be long retired before this happens, but I'll keep track of it.

MR. OLSON: I have a comment about that, and that's that it's very difficult to abandon all of the information we have about the plasma based test, and what I would hope is that as regulations are developed, that it make it possible that these other issues can be explored. I mean our history can constrain us if we let it.

MR. HILL: One last comment. People say, Jim, would you really be happy if it was just finger stick whole blood coag testing? I said no. Because it's going to be non-invasive coag in the future. So technology is not going to stop.

[Laughter.]

DR. TRIPLETT: Eric.

PARTICIPANT: I didn't know whether we should have the same standard and the same calibration and the same standard, clinical standard, for plasma and for the whole blood. We might develop a standard for normal blood and for normal plasma. But this will be impossible to convert this to a patient. The patient might have normal plasma but the patient might have, let's say, leukemic cells or activated platelets and then we have a different clinical situation, and the conclusion would be then to use a different INR

value for the patient who has, let's say, an activated blood. For this reason, I think we should not see the problem identical to plasma and to whole blood situation.

MR. OLSON: We actually talked about this issue some also, and it was also mentioned this morning related to or earlier in the afternoon about the ACT and the effect of other physiologic situations going on in the patient with hemodilution and temperature and uremia and all of these other issues that can be going on. And the problem is I think we're faced with the fact that people are going to be making whole blood instruments and those things are going to be affecting them.

PARTICIPANT: I think it's good that we hear from a manufacturer that they're excluding, trying to exclude the platelet involvement and the red cell involvement because I think from a practical standpoint, it comes out that those people who use the whole blood with the finger stick PT are using it interchangeably with the plasma measurements. And I guess if it comes out, as you point out, we have the vast experience with plasma, we shouldn't abandon that and that's the practical outcome.

PARTICIPANT: Just a note to that, I don't think there is really a pressure to develop something that is a standard. If you want to develop a whole blood assay that

you think is better than the plasma, I think you are free to do that and you can file a PMA on that and establish utility. And if it's really better than, it's easy to show. If you want to measure PT in whole blood, I think you should measure PT in whole blood because that's the intended use. So if the intended use is PT, then it has to be PT as it is defined at present. If you have a new definition, then it's available and can be done.

DR. TRIPLETT: In many of the whole blood tests, the proficiency testing program really breaks down because the only matrix we can use to send out to the user is that of the manufacturer. So we're really locked into evaluating a system and not evaluating across the board how different tests respond to a given challenge.

MR. OLSON: I can't be quiet. I have a comment about that also and that's that it may not be as easy as you say to demonstrate this. We commented in our group too that it takes really very large population studies to demonstrate these differences and they can be very expensive to do. And if one can gather information in parallel, we may learn it while we're still taking care of patients.

DR. TRIPLETT: Eric.

PARTICIPANT: Could I make a comment about the UK --

DR. TRIPLETT: Sure.

PARTICIPANT: We've been running EQA scheme in this area for about a couple of years and we've had about six or seven different surveys. And it's not perfect, but we have been sending around the same material to the users of these devices as we've sent to those using conventional laboratory equipment. And, in fact, the results are astonishingly close between the users of these devices and the INRs produced by laboratory in plasma. It's not perfect. We clearly would prefer to be using a whole blood EQA, whole blood EQA material, which we're currently working on, but just to reassure you that the stuff that we do send around to the users of these devices is very, very close to the conventional uses.

DR. TRIPLETT: Are we ready for Group Three?

DR. LaDUCA: I'm Group Two so if somebody is out there from Group Three.

DR. TRIPLETT: Does Group Three have a spokesperson?

MR. HILL: I don't want to repeat what's already been said and I think by the time we get down to Group One, there's not going to be much left to say. We had quite a few Europeans in the group, which was interesting. It was funny how they selected who went with what. We were trying to figure out the difference between aim and scope, but

basically--and we could have spent probably a half an hour on that.

But for the aim, we had two, and that was use the INR for PT's traceability of plasma and whole blood reagent systems and instruments, and it has to be traceable to the WHO. So I think that was what the first group said is that we really want to be able to trace and to know the linkages to the INR WHO standards. And we also focused primarily on PT and oral anticoagulation. The other aim, before I get down to the scope, is it was brought up by a couple of individuals, we do need to define what an acceptable bias is or what the acceptable limits of miscalibration is before we could go further with actually defining how to check and verify calibration of these devices.

And going back to scope, we talked about the need to control calibration or verification of the calibration of home PT monitors. This is going to be critical and this came up over and over with the people in my group. Made it kind of tough on me as the industry guy representing these devices, but the clinicians, the doctors, they want to make sure that these devices, once they go home, can be checked out. And how can that be done? Well, before the instruments are sold, it really should be the manufacturer's responsibility. The manufacturer should be able to test these and produce the data so that there is a high degree of

assurance that each one of these instruments will be within that acceptable bias of a calibrated meter.

Also, after the instruments are sold, we've got to have the ability to check these monitors. We can do that one of two ways. We talked about bringing the meters back in periodically. I know that's tough, but that was what was brought out by the group. I think this is employed in some countries in Europe. We even discussed what I thought was kind of interesting. Scientifically you could exchange the meters out so you don't even get the same meter back, but that might not be very popular here in the U.S. with the potential for infection or whatever. But that certainly is one way to check these meters. I think twice a year is one program in Europe.

And the other way would be to have narrower control ranges because nobody really believed that the current controls would suffice as a verification or validation of the calibration of an individual meter that's at home.

There were a couple of other considerations, parking lot issues. This was excellent that we did bring up the need for patient training, whether this in the scope of what we're trying to accomplish here to help the FDA ensure safety of these devices. But certainly training is an issue

and that goes not just for the patient but training of the doctors. We discussed that some of these problems in managing patients or lack of knowledge in what to do with an INR, these are surfacing because of the advent of the whole blood devices. But some of these problems have been out there for quite awhile. Some doctors simply are not very expert at managing these patients.

And then finally there was a comment that it's a lot of work to do all of it, and if we just stick to standardization and QC controls, that's a big enough job as it is to try to put guidelines together.

DR. TRIPLETT: Questions for Jim? Group Two now.

DR. JACOBSON: Actually I will take the liberty of just addressing one of the issues that Jim just brought up. The approach we use in my own facility for longitudinal validation is on specified intervals we have the patient come back into the facility, the patient tests on their device, the staff does a test on the patient using a patient device, and we then test the patient on the clinic device. So the patient gets three finger sticks on that day, but that way we can at least get a reasonable reference. If the patient gets two and the nurse gets four, then you're going to wonder about patient competency. If the nurse and the patient both get three on the patient device and get six on the clinic device, then you're going to wonder about the

ongoing standardization of that device. So with interval evaluations before I'd want to make a recommendation on interval, I'd like to see some data to support a given frequency of validation. But that's one approach we're using in our facility currently to address that.

In Group Two we had some of the same challenges that others did in terms of deciding what all we're going after and how we're going to address all of coag or hemostasis at one shot. Being a cardiologist and a clinician for a background, one of my own pleas is always don't look at this as testing. As Dr. Ansell pointed out earlier, managing these patients is much more than just pro time testing. And if you really want to improve the quality of anticoagulation management, at least when it comes to long-term warfarin monitoring in this country, it has nothing to do with the accuracy of pro time testing.

The big problem is the patients never get the tests done and most of the adverse events in this country are due to lack of testing, not due to inaccurate testing, and most of the medical legal exposure is due to lack of testing. Medicare numbers are that the average Medicare patient on coumadin gets four tests a year. Cheap testing but high price in adverse outcomes.

The way we kind of split things up, I do much more with coumadin than I do with heparin. So one of the other people was asked to look primarily at the heparin type issues, ACT, PTT, and my comments will apply primarily to the routine monitoring of coumadin and the PT INR. One of the initial things we came up with in our group, though, had to do with a concern about applying different standards to whole blood testing as opposed to plasma testing.

Most whole blood instruments have requirements you can only report up to a given range. You can report between up to an INR of ten or up to an INR of eight, whatever was validated. But most thromboplastin reagents come out to the central lab; you can report to whatever level you want to, and it seems that there is some differential. I'm not in the approving categories as to whether there's a differential as to how the plasma thromboplastins are evaluated and whether there's a difference in terms of what those standards are was unclear, but to have, if we're going to be comparing the methodologies to each other, to have some uniformity as to what ranges those were being applied over would be desirable.

In terms of the aim, we simply stated that we wanted to ensure that there was clinically useful accurate results independent of the testing device. Now that leaves several things to be defined: what is clinically useful and

what is accurate? Do we need third decimal place accuracy? Many labs report out INRs to the second decimal place. Should there be a recommendation that labs not report beyond the first decimal place if it's not clinically useful information? Does it give a false sense of reassurance in terms of accuracy of the test? But basically the aim of this is to ensure, that as Dr. Ansell had mentioned, the results that we get are clinically useful in managing patients.

The scope--there were a couple of areas we felt needed to be looked at, but that, as was discussed in many presentations today, the scope needed to include relevance for both the specific test, PT INR, but also for ACTs, PTTs. Each of those would have different implications as well as for the specific indication for testing.

And as was mentioned with the PTT presentations this morning, PTT is used for many different indications, different therapeutic intensities for many of those indications, and the specificities of the tests at different indication or at different therapeutic levels was variable. So to try and address what those different issues were.

In terms of the elements, one of the things that we felt was somewhat lacking at the moment what is the data currently that there is a problem with standardization and

what is the magnitude of that problem? So we didn't start off the day by saying here are five manufacturers of point-of-care devices, here's the horrible status of standardization on these devices, they were ranging everywhere from two to six on the INRs that we're reporting. This is unacceptable; we need to improve that.

So one of the first things we need to do is define what is the magnitude of the standardization problem and how big an issue is that? And once we have that data in place, then can move forward.

Our group also felt strongly that the elements of a standardization recommendation would preferably be industry based rather than local facility based. And even though there are many facilities that have research potential, can do this as well or better than industry may be able to, as was mentioned by Group Four, there are many other facilities that do not have the sophistication, and there was concern that ability to locally change the ISI and things of that sort may lead to more problems with standardization and harmonization than what they would correct.

The other that we felt fairly strongly about was that the recommendations needed to define what the resultant parameters or confidence levels would be. So if we say do the standardization process and as a result of that INRs

that are within .75 of each other are acceptable, again one of the concerns was with the INR. If anything, we oversold that in the United States, and many doctors still believe that the INR is second decimal point accuracy and I've had one case where a physician asked a patient to return his point-of-care device because it was obviously inaccurate because it was consistently 0.3 INR units off from the central lab.

So unless the standardization recommendations come out with specified definitions as to what the results of standardization should yield in terms of comparability of results between devices and methodologies, then some things would be lacking in those recommendations.

Frank LaDuca was supposed to be addressing the issues on ACT, PTT of our group. Frank, any other things to add? One other thing, as he's coming to the microphone, there was a request that we actually look into some other surrogate markers, i.e., to what extent can actual factor levels be used within a standardization process? So rather than simply looking at INRs and how do we calculate the INRs to each other, can we say this INR correlates to these given factor levels and use some of those methodologies or are there other surrogates that could be utilized?

DR. LaDUCA: Yeah, the group was focusing on the issues that Alan laid out there for all three tests for the most part. There were a couple specific aPTT and ACT issues, one of which was should there be whole blood standards generated for the aPTT in lieu of, you know, plasma based equivalents because you just complicate, by having correlations involved, you complicate the irreproducibility, the variability of the tests. So we were looking from an aPTT perspective for that and also with ACTs and aPTTs to keep it very clinical application specific.

In other words, aPTTs for heparin monitoring have to be clearly defined in that parameter and not trying to complicate it with looking at aPTTs for coagulation deficiency. But, in general, the comments that Alan put together for the PT hold true for most of the other tests.

DR. TRIPLETT: Comments? Thank you. Very good.

MR. HILL: I did have one comment. I'm sorry, but this is my chance. Dr. Jacobson was talking about the high INRs and the lab is allowed to report very, very high INRs, but all of a sudden I'm hearing things that these whole blood devices will be cut off and you won't have a high INR displayed, you'll only have out of range. Well, I agree totally. You really don't know much difference between a six and nine INR. It's meaningless really, but within one patient, within one instrument, with this device, there

really may be a difference between a nine and a six, and you can use that as you bring your INR down.

But what I'm afraid of is that we won't have that, the patients won't have that and the doctor won't have that, because it will just cut off at five or whatever. I see this as it bothers me. Not much bothers me anymore because I've been there too long, but this is kind of getting to me. So do you have any comments on--you personally, would you rather have INR--

DR. JACOBSON: Clinically for me that's an issue. I think all of this is an issue. Our current sophistication in anti-coag is very, very primitive despite all the advances we have. Our understanding of what the therapeutic ranges really should be, what is the optimal frequency of testing, there's a lot of things that we still need to sort out. The difference between an INR of nine and an INR of 14, it's rarely going to change clinically how I approach a patient. So I don't need to have things within--I don't need to have second decimal place accuracy at that end of the range. I know that there is a lot of uncertainty when I hit that end of the range. That's a patient, though--and I've often joked that all I really need is tell me are they low, therapeutic, or high, and I'll take care of them.

MR. HILL: So to you a 14 and a five would make no difference within one patient as they gain experience?

DR. JACOBSON: No, no. A five and a 14 will make a difference. And there's probably a difference between a 12 and a 25. Is there a difference between a 12 and a 14? Probably not. So I'm not going to get the same level of resolution at that end of the scale, but I would like to have the numbers and especially when I'm using point-of-care in an anticoagulation clinic to say that every patient with an INR above six I now have to send up to the lab and have a venous draw done doesn't make a lot of sense to me.

I want to be able to do the routine management on 99 percent of my patients with the same system. Now on the patients doing home testing, you essentially never get that high because with the increased frequency of testing, you pick up the destabilization in the INR long before you get to 12 because they're going two, four, six, eight. If you haven't reacted by then, you're probably never going to, but the increased frequency of testing brings a whole lot of additional value to your ability to manage these patients.

DR. TRIPLETT: So are you saying the more you test, the less costly it is to the system? Preventing complications?

DR. JACOBSON: Your testing costs may go up, your management costs may go down.

DR. TRIPLETT: Right. But the net is a positive?

DR. JACOBSON: Yes.

DR. TRIPLETT: Right.

DR. JACOBSON: But maybe not to the lab if the lab is having to bear the cost of the testing, and you haven't figured out a way to cost shift between the services.

DR. TRIPLETT: Well, we won't go there.

[Laughter.]

DR. TRIPLETT: Group Number One.

DR. MIZE: We felt that task one was to improve patient outcomes. This is a very general statement. The results accurately reflect the patient's condition accurately and that we also felt that we defined that there was a need for standardization of whole blood clotting times and to develop a process by how it is done.

I guess the scope--PT, we need to establish material and method for INR ISI calibration. For ACT and PTT, there was a need to start going in this direction, but it wasn't as definite as with the PT or the possibility that it could be done.

And then task three, how is this going to be done? With PT use the WHO Calibration Reference method and material. And there was felt a need to develop a simpler procedure to calibrate individual monitors or for looking at

home testing. And how do you handle all the different units that are going to be out in the field? And so this part in checking has to be less complicated than developing the original ISI of the material and the instrument. I'll be happy to have anyone in my group add to that.

DR. TRIPLETT: Questions? If you would like, there could be a public comment period. Leon, you can start off.

DR. POLLER: I just wanted to add something to the group. We divided tests into the PT which has a calibration system, which is standardized, and all the other tests which haven't. And all the other tests which haven't, we said they should be devising reference materials such as WHO prepared for the APT, the anti-Xa assays, and ACT anti-Xas, that sort of material, referenced heparin standards.

DR. TRIPLETT: I think it's important to appreciate the difference between a control, a reference material and a standard.

DR. POLLER: Yes.

DR. TRIPLETT: And we have very few standards, some reference materials, and controls for most everything that we do.

DR. POLLER: Yes, yes. But regardless, it's an impossibility to standardize all the methodology for all the other tests in view of the multiplicity of instruments.

We'll never get those standardized, so you need reference materials, whatever is available nationally to do that. Quality control materials, too, come into that.

DR. TRIPLETT: Yes. Other comments? Gail.

Ms. MACIK: I think to kind of summarize some of the things I've heard, one of the things that I keep coming back to is the clinical and we, in a meeting like this, you have meetings of minds, and one is 60 years of experience with a PT system, but in the clinical world, if we're going to use whole blood, we have to think outside the system and that's what was brought up. You know how do we then think outside of the system and it's going to be very difficult to put the same kind of controls and same kind of laboratory science to a whole blood system which is part of the reason the whole blood system wasn't developed in the first place when we went to plasma because plasma allowed you to do it.

Now we're going backwards and going to a whole blood system. So we have to go back and say, okay, what are we going to do with it? So the aim, you know, we have to have something that's out there that clinically you think you're doing--your standards are even. Okay. There's harmony between the instruments. Regardless of what instrument you do, you're doing about the same kind of clinical management of a patient, but unfortunately all of

that has to still be defined, you know, what are the goals, what are the things we have to do?

We don't understand anticoagulation now and if a group like this that has an interest in anticoagulation can't come up with exactly what they mean on things, the people in this country that are really managing it aren't coagulationists. And they don't understand at all, as was pointed out, you know, a difference of a .3 INR, that's nothing. But we don't have education out there. So we don't know how to use our current system.

We're going to a system that may be better if for no other reason that it points out all the deficiencies we have in our current systems and then we can kind of try to put all this together, and I think we ought to be aiming towards a more generalized approach: sub-therapeutic, therapeutic, super-therapeutic, and how do we, where do we come up with those ranges and, you know, try to really look at that. If we tie into seconds, if we tie in for these instruments, then we tie ourselves to something that may not be met by all instruments.

Right now the whole blood instruments, the clotting time that they get is nowhere, you know, it's manipulated, it's put into formulas, it's made to look like something else, and there's a lot of, you know, you're not letting it really say what it is, we're really forcing it

into to act like what we want to see. So to summarize my ramblings, clinical has to count. The endpoint is are we managing all the people clinically the same and are the instruments out there all allowing a person to be clinically managed about the same, and they're not changing over time with that instrument, that you're getting about the same results with these.

And the "about" is an important aspect because we'll never be exact with these and the way that we know whether or not we're managing them right is that part of the QA of this entire system has to be did the patient's dose change, did they have any adverse effects, and then looking at the trends that the patient has, and that's more important than liquid controls or anything else on the instrument. It's really looking at all of that information and going back in.

DR. TRIPLETT: I think patient outcome is obviously the best quality control and that would be bleeds or rethrombosis and percent of time in the therapeutic range. Those are relatively easy to document. Other comments? Eric.

PARTICIPANT: Thank you. I'm not sure if it's appropriate for me to comment. I just wondered if it's a problem here in the U.S. I can't understand the doom and

the gloom about all this. We just heard that we don't know much about it, but I would disagree with that. I know Leon Poller--he hasn't asked me to say these words--was largely instrumental in setting this up. We know a great deal about warfarin, its effect on Vitamin K dependent clotting factors. The INR system is certainly not perfect. It's certainly the best.

And when we talk about patient outcomes, we know a great deal about patient outcomes. There have been some very detailed sophisticated studies. Fritz Rosendahl [?] in the last few weeks has estimated if we have to do it all again with patients using near-patient testing devices, we'll need to study something like 30,000 patients. Do you think we're going to be able to get 30,000 patients on self-testing programs because they're on self-testing programs for very good reasons. They want to be away from doctors and away from hospitals. We can't possibly find 30,000 and put them into control studies to discover outcomes that we already know.

It might not give the same results. I think probably it doesn't, but we do know enough already--I'm sure the manufacturers do; we certainly do--about the results. Samples tested in parallel are really very close, not the same, but very close. So I would disagree. I think we know a great deal about it. We know a great deal about clinical

outcomes. I think the problem is not the near-patient testing devices. I think it's largely inexperienced doctors.

DR. TRIPLETT: I would tend to agree. I think your organization is probably more centralized than in the United States in the sense that you have clinics. We have clinics as well, but many of our patients are followed by a physician who may only see five or six patients at any one time in his or her practice that are on oral anticoagulants so they're not comfortable with it. So an anticoagulant clinic is a very important piece of it in terms of patient outcome. Other comments? Yes.

PARTICIPANT: I'd like to make a couple of remarks on behalf of ISO TC-212, and I'm not sure if this is the right time to do it. It would be expanding the topic of what has been discussed so far. Should I do it now or do--

DR. TRIPLETT: Please.

PARTICIPANT: Or do you want me to do it later?

DR. TRIPLETT: Please do it now.

PARTICIPANT: Okay. We have discussed a lot about standardization in in vitro diagnostics, specifically in anticoagulation. You may be aware of the fact that ISO, the International Standard Organization, has a technical committee, TC-212, that deals with standardization in in

vitro diagnostics. How that came about I could tell you, but you'd have to give me another ten minutes and I'm not sure if you want to do that. So let me concentrate on what ISO does, ISO TC-212, in particular, does. Among 15 other projects, standardization projects for in vitro diagnostics that they have, and among those some that have been mandated as harmonized standards by the European Commission in support of the in vitro diagnostic medical device directive, among all those projects is one specific project that has relevance to this group, and the topic of that project is specifications and standards for instruments for point-of-care and self-testing in monitoring of anti-coagulation treatment.

And there is yet another project in CEN TC-140 which deals with IVD standardization in support of the IVD directive and that is general requirements for self-testing devices. I'm mentioning this to you for two reasons. First of all, it would be great if the standardization efforts that come out of this group could be in some way coordinated with what ISO TC-212 and CEN TC-140 do. ISO TC-212 and CEN TC-140 have a very close coordination. So that is taken care of.

But if this group, if ISTH is going to become active in standardization of anticoagulant in vitro diagnostic medical devices, then please help us to

coordinate what is done in this group with the efforts that are already underway, particularly in ISO TC-212.

The second concern that I have is rather an appeal on there is so much expertise in this group among the attendees of this meeting, that I became kind of jealous to what you are doing here. We are fighting for expertise. We are trying to get the people who have the knowledge to develop these standards into ISO and into CEN so that the standards that we develop will be meaningful, will be useful, not only for industry but also for users and for regulators. And my appeal to you people is please participate in the work that will be done here in ISTH but also in the work that is going to be done in ISO TC-212. It will be most helpful and I personally believe it's very important. Thank you very much.

DR. TRIPLETT: Thank you. Any other comments? Alan.

DR. JACOBSON: Again, just trying to draw parallels between plasma testing and point-of-care testing. Inovin was kind of an interesting reagent when it came out. When we first started using, it seemed like it came on to the marketplace without too much trouble, but then there were some questions afterwards. My guess is that using low ISI reagents has probably caused as much confusion in caring

for patients as the use of point-of-care devices. An example, one laboratory that I was asked to consult with, the medical staff had literally threatened to boycott the laboratory unless they would remove Inovin because half the docs were still looking at the pro time in seconds even though they were getting both results.

So I think one of our big challenges is trying to again sort out the educational aspects of things from the actual technical scientific aspects of things. Where we need more education, we need to work on more education. Where we need people to understand what is the really effective relevant differences in INRs, we need to work on educating on INRs. When should you use an INR instead of a pro time? There's a lot of different anticoagulation issues, hemostasis issues, that we need to make sure are clarified and educated, but all of the different aspects bring those implications with them, and I'm not sure there's too much unique to point of care. It's another methodology, but I'm not sure there's that much that is totally unique about that compared to introducing low ISI thromboplastins or some of the other types of changes we bring about.

DR. TRIPLETT: Thank you. Certainly there are pockets of ignorance here and there and those need to be addressed. Other questions?

Well, I'll close with just a few comments. In 1977, when I--I think it was the second ISTH meeting that I went to, Neils Bang came up to me and he said I hear you're on the anticoagulant committee, and I said that's right, and he said you have a lifetime job. That was the PT. And I think it remains the same. Eric is now closely associated with that committee and we'll hear more about that, I guess, on Sunday. So I think the PT remains a challenge and we talked today about some of the issues.

Some of these issues are matrix based in terms of proficiency testing. Some of the issues have to do with differences between various devices and how they're employed. I think the outcome, the patient outcome, however, is the most important issue and certainly there are studies now which verify the fact that patient testing leads to a better outcome that using a central laboratory. So I think that's an advance. Not every patient can do self-testing. Certainly there are patients who wouldn't qualify, but for those who can I think it's a major opportunity for them.

With respect to the aPTT, I don't think we made very much progress in terms of trying to identify what to do with near-patient APT testing, the problem being I think the aPTT has multiple uses, much more so than the prothrombin

time which really at this point I would say the vast majority of tests in the United States that are done for the prothrombin time are done to monitor oral anticoagulation.

On the other hand, the PTT, probably the most common use is heparin monitoring. Although it may be close, the second most-common use may be preoperative testing which still is around and people are still using it. And occasionally they uncover patients who indeed have an abnormal aPTT preoperatively. So the vast majority, however, I think are still in those two categories, heparin and preoperative testing. Perhaps the lupus anticoagulant has made an impact on the aPTT, but with the use of the DRVVT and the realization by most people that multiple tests are needed to rule out a lupus anticoagulant, people are ordering aPTTs, DRVVTs and perhaps hexagonal phase neutralization as an approach to that diagnosis.

So the PTT and factor deficiency still is used in terms of identifying patients with factor deficiencies and again that is usually picked up with preoperative screening and it's serendipitous observation in many cases. The last one that we saw that was significant was recently a gentleman who had a baseline PTT of 130 seconds and it turned out that he was prekallikrein deficient. So he had absolutely zero prekallikrein, but that's irrelevant with respect to clinical bleeding.

I think one other important aspect of this discussion today was the diversity of the audience in the sense that we have people from industry, we have people from the regulatory agencies, we have people from the standardization committees, interested clinicians, and as a consequence I think the exchange of information, which has already been emphasized, has been a very good exchange from different groups, different perspectives.

This kind of meeting, I think, is very valuable in terms of advancing our overall mutual understanding of what the problems are, and I hope that there are opportunities in the future for similar meetings. And with that, I'll turn it back over to Ginette. I would like to thank Dr. Michaud for her organizing the meeting. She's done a wonderful job in putting together the various groups that are here today and I congratulate her.

[Applause.]

CHAIRPERSON MICHAUD: Just a few final words. I want to thank you all very much for attending this session today. I think that we made an important first step in developing what I hope will ultimately be improved performance of these assays and improved use of these assays by the clinicians. I think we'll call it a day. I know that most of you will be attending the ISTH meeting in the

coming week and so you have still much work ahead of you. Thank you again for attending.

[Applause.]

[Whereupon, at 5:40 p.m., the meeting was adjourned.]